Movement Disorders
CLINICAL PRACTICE

Apomorphine at the End-of-Life—A Role to Play

Carolina Azoia, MD,* Catarina Borges, MD, Ana Graça Velon, MD, and Rita Raimundo, MD

We read with interest the recently published systematic review by Castillo-Torres and colleagues[1] on the last 30-years of use of intermittent subcutaneous apomorphine (SCA) for *off*-period rescue in patients with Parkinson's disease (PD). The authors described great motor improvement and remarkable reduction in daily *off*-periods. Their work showed that SCA promptly and effectively reverses refractory *off*-periods and serves as a useful resource in patients with motor fluctuations such as two or three predictable *off*-periods a day, sudden/unpredictable *off*-periods, disabling morning akinesia, postprandial *off*, or wearing-*off* phenomena. We wish to share our experience with the use of SCA to relief *off*-periods in patients under palliative care because, although there was no mention to this approach in the Castillo-Torres review, our patient's response (including the fact that daily intermittent injections have not led to long-term worsening of dyskinesia or significant neuro-psychiatric symptoms) suggests that the substantial effect of SCA on his *off*-periods and overall quality-of-life is in agreement with such results and in line with many decades of experience of the authors.

Non-motor symptoms dramatically impact the quality-of-life of patients with PD, especially at late-stages. Because patients may be afflicted by non-neurologic conditions that hamper the management of treatment options, optimizing medication became an important aspect of end-of-life care.[2,3] We hope to open the room for discussion about how far can neurologists go in helping relieve PD patients from their physical pain and suffering.

A 70-year-old right-handed male presented to the Movement Disorder Outpatient Clinic complaining of worsening abnormal posturing of neck and hands, difficulty swallowing, and severe chronic pain. He had been diagnosed with PD 10 years prior and reported increasingly frequent sudden *off*-periods of anarthria, severe dysphagia, severe abdominal pain, and inability to walk. He suffered from delayed-*on*, wearing-*off* and no-*on* phenomena, peak-dose dyskinesia of the trunk and lower limbs, and nocturnal akinesia, and had been referred to palliative care because of severe abdominal pain and constipation without structural disease. He was on levodopa/carbidopa/entacapone (150/37.5/200 mg 5id), levodopa/carbidopa prolonged-release tablets (200/50 mg id), safinamide (100 mg id), transdermal rivastigmine (4.6 mg id), and clozapine (25 mg id). Examination revealed asymmetrical akinetic-rigid parkinsonian syndrome, cervical dystonia, dyskinesia involving the trunk and lower limbs, and small-step, unstable gait (Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS]-III, 74; Hoehn and Yahr scale 4). Neuro-psychological evaluation concluded for mid-stage PD-associated dementia, hypersexuality, punding, visual hallucinations, and persecutory delirium were documented. His cognitive profile contra-indicated deep brain stimulation of the subthalamic nucleus and apomorphine perfusion, therefore, we opted for SCA at *off*-periods, particularly before meals to aid with dysphagia and allow feeding. The initial dose was 2 mg, 2–3 times a day (daily dosage of 4–6 mg), because 2 mg was the dose to which we observed a significant reduction of the MDS-UPDRS-III (from 74 to 46). To prevent nausea, domperidone 10 mg 3id was introduced 3 days prior to the trial, remaining through the first 15 days of treatment. There were no bothersome dyskinesias or psychiatric symptoms; however, family members noted mild cognitive difficulties. Encouraged by such improvements, we raised the dose to 3 mg at *off*-periods with no major side-effects (no additional cognitive decline nor psychotic manifestations). These benefits lasted after the pharmacological regime was simplified (levodopa/carbidopa/entacapone was replaced by levodopa/benserazide 200/50 mg and safinamide was withdrawn). The overall response was remarkable with notorious gains in speech articulation and autonomous walk for short distances. However, the most impressive outcomes occurred on rigidity, dystonia, pain control, and dysphagia, 15–20 minutes post-SCA; rigidity and dystonic postures became less severe, with less pain and discomfort, allowing a decrease of on-demand morphine dosage. The patient was no longer unable to ingest liquids/solid food at *off*-periods, an aspect he and his wife (his caregiver) considered the most valuable achievement. Nine months after the introduction of SCA, he maintains rescue

Neurology Department of the Centro Hospitalar de Trás-os-Montes e Alto Douro, Vila Real, Portugal

***Correspondence to:** Dr. Carolina Azoia, Centro Hospitalar de Trás-os-Montes e Alto Douro, Serviço de Neurologia, Avenida da Noruega, 5000-508, Vila Real, Portugal; E-mail: carolinazoia@hotmail.com
Keywords: apomorphine, end-of-life, end-of-life care, palliative care, Parkinson's disease.
Received 30 May 2023; revised 29 September 2023; accepted 2 October 2023.
Published online 2 November 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13907

Video 1. Neurological examination. Patient performing neurological examination. We see an akinetic-rigid parkinsonian syndrome, with a left predominance, with no major tremor or facial/cervical dystonia. There is still some slight bradykinesia in the finger tapping and the supination-pronation maneuvers of the hands, as well as dysdiadochokinesia, especially on the left side. No dyskinesia is seen during neurological examination.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13907

Video 2. Gait examination. The patient is able to lift from the chair with no major help, showing an initial freezing. The gait discloses a shuffling pattern, with small steps and fragmented turns, associated with an anterior-right flexion of the trunk.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13907

injections 3 times a day (Videos 1 and 2 illustrate his condition at present). We understand that this could mean a need to proceed to continuous subcutaneou infusion, which has not been yet considered to avoid further cognitive decline/behavioral changes. After a small period at a palliative care unit, the patient is stable and at home.

Cognitive decline did not figure among the most frequent side effects reported by Castillo-Torres et al,[1] indicating that the impact of apomorphine on cognition is probably overrated, with benefits justifying the risks to some extent. As our patient had a history of hallucinations, apomorphine dosage was carefully titrated, although these complications have rarely been reported, because of apomorphine's antagonism of 5-HT2A receptors.[1]

Despite the growing emphasis recently being given to the role of palliative care in advanced PD, there is still much to be done, especially with regard to chronic pain, mood swings, or dysphagia, because there are few therapeutic options available for these patients.[4,5] Early palliative care focuses on minimizing dyskinesia and decreasing occurrence of *off*-periods in an effort to maximize independent motor function.[4] Later stages treatment focus on treating non-motor symptoms and having a more supportive approach.[4] To our knowledge, there is only one report of apomorphine providing symptomatic relief in terminal PD patients.[2] Our case highlights the potential benefits of SCA for symptom control at the end-of-life and supports its consideration in advanced-PD patients under palliative care.

Author Roles

(1) Project: A. Conception, B. Data collection. (2) Manuscript: A. Writing of the First Draft, B. Execution, C. Review and Critique.

C.A.: 2A, 2B
C.B.: 1B
A.G.V.: 2C
R.R.: 1A, 2C

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Informed consent was obtained and signed by the patient, who fully understood the scope of this manuscript. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: No specific funding was received for this work, and the authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for previous 12 Months: The authors declare that there are no additional disclosures to report. ■

References

1. Castillo-Torres SA, Lees AJ, Merello M. Intermittent apomorphine use for off period Rescue in Parkinson's disease: a pragmatic review of over three decades of clinical experience. *Mov Disord Clin Pract* 2023;10(2):190–208. https://doi.org/10.1002/mdc3.13593.
2. Dewhurst F, Lee M, Wood B. The pragmatic use of apomorphine at the end of life. *Palliat Med* 2015;23(8):777–779. https://doi.org/10.1177/0269216309106979.
3. Oliver D, Veronese S. Specialist palliative care for Parkinson's disease. *Ann Palliat Med* 2020;9(1):S52–S62. https://doi.org/10.21037/apm.2019.12.01.
4. Lokk J, Delbari A. Clinical aspects of palliative care in advanced Parkinson's disease. *BMC Palliat Care* 2012;11:20–28. https://doi.org/10.1186/1472-684X-11-20.
5. Hvisdak V, Huang AP, Kluger BM. Palliative Care of end Stage Parkinsonism: an overview including the five pillars framework. *Mov Disord Clin Pract*. 2022;10:1–5. https://doi.org/10.1002/mdc3.13620.