

APOMORPHINE INJECTION FOR MORNING AKINESIA IS RAPID AND RELIABLE: MANAGING DELAYED ONSET OF FIRST DAILY ORAL LEVODOPA DOSE IN PATIENTS WITH PARKINSON'S DISEASE

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In patients with Parkinson's disease (PD), motor and non-motor symptoms are frequent during OFF periods, especially when the next levodopa dose has a delayed onset of action (delayed ON). The treatment of PD motor symptoms relies on oral levodopa, which must be emptied from the stomach and absorbed in the proximal small intestine. Gastroparesis causes delayed gastric emptying of levodopa with a delay in its delivery to the small intestine, resulting in the clinical phenomenon of delayed time-to-ON (TTO) after a levodopa dose. Initially, the therapeutic effect of each levodopa dose is rapid, reliable and sustained (i.e., onset around 20 minutes and a long duration response). However, after several years of levodopa treatment, the long duration response becomes replaced by a short duration response, and OFF periods emerge. While OFF periods can be improved with multiple adjunctive medications, delayed TTO of the next levodopa dose can still significantly increase OFF period duration. Medications used to treat PD also contribute to GI dysfunction, including levodopa, dopamine agonists, anticholinergics, amantadine, and inhibitors of MAO-B and COMT.

Gastroparesis, where the stomach takes longer than normal to empty, is common in both early and advanced PD, and may even be a marker of pre-clinical PD. Symptoms of gastroparesis can overlap with adverse effects of PD dopaminergic medications. Gastroparesis may result in a variety of GI symptoms, including nausea, postprandial bloating, abdominal discomfort, early satiety, vomiting, weight loss and malnutrition. In addition to causing GI symptoms, gastroparesis in patients with PD may also cause motor fluctuations. Several studies have demonstrated a significant relationship between gastric emptying and levodopa pharmacokinetics in PD patients, by delaying the arrival of oral levodopa to intestinal absorptive sites. The effect of delayed gastric emptying and impaired intestinal absorption on oral delivery of levodopa can result in delayed-ON, morning akinesia, suboptimal-ON, and dose failure (no-ON). Delayed-ON of the first daily dose of levodopa results in morning akinesia. Morning akinesia is common, debilitating, and can be prolonged due to a delay in gastric emptying, impaired intestinal absorption, or pharmacodynamic effects. Morning akinesia can have a significant impact on quality of life (QoL) and delay normal daily activities. Yet morning akinesia is underreported by patients, under-recognized by physicians, and thus can remain undertreated for years.

Therapeutic approaches for managing morning akinesia remain suboptimal, mainly due to the effects of gastrointestinal (GI) dysfunction delaying the onset and consistency of levodopa dose onset. Treatment strategies to improve morning akinesia focus on reducing early morning akinesia (through the use of a long-acting dopamine agonist or by inhibiting MAO-B) or on attempts to hasten TTO by enhancing delivery of levodopa to the proximal small intestine (through the use of liquid, dispersible, modified, or higher-dose levodopa). Alternatively, delivery of dopaminergic therapy by a non-oral route may be useful in patients with GI dysfunction who experience these motor fluctuations.

Delivery of dopaminergic therapy by a non-oral route is important to consider in patients with PD and morning akinesia. Apomorphine is a potent dopamine receptor agonist that can be administered subcutaneously. Subcutaneous apomorphine has a rapid onset of action when used for OFF periods in patients with PD, resulting in significant improvement of motor symptoms by 10 minutes versus placebo. Since subcutaneous injection avoids the oral route, apomorphine injection may be helpful to treat morning akinesia since its TTO should not be affected by delayed gastric emptying or impaired intestinal absorption. The ongoing Phase IV, multicenter, open-label trial AM-IMPAKT (Apokyn for Motor IMProvement of Morning Akinesia Trial) is investigating whether subcutaneous apomorphine injection upon awakening can provide rapid and reliable improvement in motor symptoms in PD patients with morning akinesia. Interim analysis of the initial 50 patients in the AM-IMPAKT trial revealed that morning akinesia is common and occurs throughout the course of PD, extending 36-48 month duration despite adjunctive therapies. Patients had never used apomorphine injection to treat morning akinesia, despite having prolonged duration of morning akinesia and with the apomorphine pen injection being available for decades. Apomorphine pen injection significantly improved the primary endpoint of TTO, and was highly reliable with 96% of patients achieving a significant reduction in TTO. Pen injections were overall well tolerated, and improvement of morning akinesia was also reflected on measures of global improvement and QoL.

These interim results from the AM-IMPAKT study suggest that morning akinesia is a common but under-recognized symptom of PD. Subcutaneous apomorphine pen injection results in a rapid and reliable TTO in these patients with significant improvement in QoL. The AM-IMPAKT trial provides evidence to support the efficacy and tolerability of apomorphine injection for morning akinesia. Subcutaneous apomorphine injection can be used by patients to provide a rapid and reliable TTO, bypassing the effect of GI dysfunction. Subcutaneous apomorphine pen injection seems underutilized by many patients and their physicians, but its use should be routinely considered for the management of morning akinesia.