

Apomorphine and Levodopa Infusion Therapies for Advanced Parkinson's Disease

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Continuous infusion of levodopa or apomorphine provide constant dopaminergic stimulations are good alternatives to deep brain stimulation to control motor fluctuations in patients with advanced Parkinson's disease (PD). Apomorphine provides motor benefit similar to dopamine, but its long-term use is limited by compliance, mostly injection site skin reactions. Administration of levodopa/carbidopa by continuous duodenal infusion allows replacement of all oral medications and permits achievement of a satisfactory therapeutic response paralleled by a reduction in motor complication severity. However, this procedure is more invasive than apomorphine as it requires a percutaneous endoscopic gastrostomy. Clinical experience with infusions shows that continuous dopaminergic stimulation of dopaminergic medications reduces dyskinesia and widens the therapeutic window in advanced PD.

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Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder, characterized by bradykinesia, tremor and rigidity with postural instability developing later in the course of the illness along with gait and balance abnormalities.¹ The motor symptoms associated with PD arise primarily from dopamine deficiency, although other neurotransmitters are involved. Treatment of PD is mainly symptomatic even if recent evidence from the rasagiline trial (ADAGIO) suggests that a disease modifying effect can be achieved particularly in the early phases.² Initial treatment aims at replacing dopamine through the administration of oral levodopa or dopamine agonists.³⁻⁶ Although oral therapy can significantly improve clinical features for many years, motor response complications (MRC), characterized by 'wearing off' and dyskinesias (potentially associated with OFF-period dystonia), emerge in up to 80% of patients. Their development leads to worsening disability with a significant impact on patient and caregiver quality of life. Moreover, non-motor symptoms (such as urinary disorders, severe anxiety, mood swings, difficulty in concentration, hyperhidrosis, itching and fatigue) may also have a considerable impact on patient and caregiver quality of life particularly in advanced patients. Finally, several axial motor symptoms-e.g. gait problems, postural instability-and some non-motor symptoms-e.g. dysarthria, dysphagia, pain, diplopia and urinary urgency-are not responsive to dopamine replacement therapy (DRT) and likely related to degeneration of in non-dopaminergic neurons.⁷⁻¹²

Possible risk factors for the development of MRC include a younger age of onset, daily dose of levodopa therapy and duration of levodopa therapy. Current evidence also suggests that the mode of oral levodopa administration (resulting in pulsatile stimulation) may be an important contributing factor for MRC.^{10,11} Substantial evidence now argues against levodopa neurotoxicity.¹³

This overview provides an update on infusion therapies currently used to provide symptomatic control and reduce MRC in patients with advanced PD. The infusion of dopaminergic drugs achieves steady plasma levels and this can help control MRC in advanced patients. The

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avoidance of plasma fluctuations helps to minimise dyskinesias since pulsatility may play a role in their mediation.¹⁴⁻¹⁷

Background for Infusions to Control Medical Research Council

Although the precise molecular mechanisms underlying the development of MRC are debated, the following points are generally accepted:

- 1) Dyskinesias appear almost exclusively in patients on levodopa therapy;
- 2) There is a relationship between dyskinesia and levodopa dosing;
- 3) There is a time lag between the levodopa initiation and emergence of the motor complications and this is likely related to severity of dopamine denervation.

Of several possible mechanisms proposed, central, rather than peripheral (e.g., relating to dietary proteins and/or the gastric absorption of levodopa), mechanisms are currently the most compelling. It is established that standard doses of levodopa/carbidopa do not restore basal ganglia physiology to normal functioning. The administration of intermittent doses of a short-acting formulation of levodopa (which has a relatively short half-life of about 50 minutes and 1.5 hours in combination with carbidopa) results in large and uncontrolled oscillations in striatal dopamine levels. Such oscillations may increase with PD progression and also with loss of striatal dopamine terminals that can normally store dopamine and buffer the inevitable fluctuations in plasma concentration observed with oral levodopa. These events change the normal physiologic situation, where striatal dopamine receptors are continuously exposed to dopamine, to one in which they are exposed to pathologically high and low concentrations of dopamine. This results in pulsatile stimulation of dopamine receptors, and the consequence of this is further destabilization of the basal ganglia network that is already abnormal in patients with PD.¹⁷⁻¹⁹

The impact of pulsatile stimulation of striatal dopaminergic receptors is further supported by experiments on 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP)-treated primates. Repeated administration of levodopa or other short-acting dopamine agonist drugs, leads to the onset of marked involuntary movements over a relatively short period of time. In contrast, treatment with long-acting dopamine agonists leads to a much lower level of dyskinesia. In MPTP monkeys, administration of multiple small doses of levodopa in conjunction with the peripheral Catechol-O-methyl transferase (COMT) inhibitor entacapone removes much of the pulsatility of motor function seen with standard levodopa treatment regimens and, at the same time, results in a lower incidence and intensity of dyskinesia. Furthermore, the addition of multiple small doses of levodopa plus entacapone to dopamine agonist treatment also

avoids dyskinesia induction in MPTP-treated primates.^{16,20-23}

It is thought that pulsatile stimulation of striatal dopaminergic receptors induces downstream changes in proteins and genes, causing plastic changes and consequent alterations in striatal output that promotes the development of MRC.¹⁸ Evidence suggests that chronic intermittent stimulation of normally tonically active dopaminergic receptors brings about alterations in cell signals in striatal dopaminergic medium spiny neurons.^{16,24} This may potentiate gamma-aminobutyric acid (GABA)-ergic efferents, particularly, glutamate receptors of the N-methyl-D-aspartate (NMDA) subtype. In support of this, overactivity of glutamatergic systems in the basal ganglia has been observed in patients experiencing levodopa-induced dyskinesias (LID),²⁵ while higher internal *globus pallidus* GABA_A receptor content has been observed in post-mortem samples of levodopa-treated dyskinetic patients compared with non-dyskinetic patients.^{26,27} Abnormalities in other non-dopaminergic transmission such as serotonergic, α_2 -adrenergic, opioid and cannabinoid mechanisms, in both priming and expression of LID, have also been reported but their clinical relevance remains to be determined.^{24,28}

The overall hypothesis that pulsatile stimulation of striatal dopamine receptors contributes to the development of levodopa-associated MRC has led to a paradigm shift in the treatment of PD following the development of therapeutic strategies that aim to minimize MRC by providing more continuous dopaminergic stimulation (CDS).^{18,29-33} It is believed that the prevention of MRC may be due to the CDS induced by constant levodopa levels, as this avoids the low plasma levodopa-trough levels seen with oral levodopa. Based on clinical evidence, additional potential benefits of CDS include alleviating nocturnal disturbances, avoiding priming for motor fluctuations and dyskinesia, minimizing daytime sleepiness, preventing the development of gastrointestinal dysfunction and reducing the risk of developing psychosis or behavioral disturbances.^{30,31,33}

Apomorphine

Apomorphine is the oldest dopaminergic medication and was initially known for its emetic properties. It has been applied in several medical conditions such as analgesia, insomnia, alcohol dependence, schizophrenia and others. It was initially used for PD over 60 years ago but later ignored for many years following levodopa introduction. It is also the most potent dopamine agonist and its administration can provide symptom relief comparable to levodopa. Apomorphine exerts its antiparkinsonian effect by direct stimulation of striatal postsynaptic dopamine D1 and D2 receptors.³⁴ The drug has a rapid absorption after injection (C_{max} 20 min), and a short half-life (almost 43 min), and this is consistent with its rapid onset of action, with effects apparent within 5-15 minutes of subcutaneous administration. Clinical studies generally support a

role for CSAI as an effective option for patients with PD and severe fluctuations, poorly controlled by conventional oral drug treatment. Overall, studies report an improvement in OFF-time between 50% and 80% as well as dyskinesia.³⁴⁻⁴⁰ However, these results were reported several years ago in uncontrolled conditions and mostly in individuals on levodopa mono-therapy before other oral dopamine agonists had reached significant clinical application. While the benefit on off time is consistent across all studies, dyskinesia improvement is somehow controversial. Widespread use of dopamine agonists since early disease stages usually leads to a reduction of levodopa doses, the main contributor to the development of involuntary movements. Dyskinesia reduction generally occurs after a few weeks or months of continuous dopaminergic stimulation as a result of wider therapeutic window. Finally, apomorphine mono-therapy can be achieved only with high doses (usually >100 mg/day) at a price of high risk of behavioural adverse events. Association with oral levodopa (most common condition in clinical practice) de facto does not abolish pulsatility and prevents benefit on dyskinesia.

Intermittent subcutaneous apomorphine (penjet) may also be suitable for the long-term acute treatment of OFF episodes in patients with advanced PD.^{41,42} Apomorphine injections can be a particularly useful option also in patients who undergo surgical procedures or to treat additional non-motor symptoms like dysphagia or pain occurring during OFF periods.

Our experience refers to a prospective study where we compared the effects of CSAI ($n=13$) with STN-DBS ($n=12$) in patients with advanced PD and motor fluctuations and dyskinesias that could not be controlled with standard oral treatment.⁴³ Patients were given the choice between the two treatments and many chose apomorphine infusion due to the long waiting list for the DBS surgical procedure. Clinical and neuropsychological outcomes were measured 12 months after initiation of treatment. With apomorphine, patients had a 51% reduction in daily OFF-time and were able to reduce their levodopa dose by 29% at 12 months.⁴³ There was no significant change in the abnormal involuntary movement scale (AIMS) scores, suggesting that apomorphine was not an effective treatment for dyskinesia. Neuropsychiatric testing revealed no significant changes in cognition or behaviour, a finding in agreement with other studies.^{44,45} Among patients who received STN-DBS for 12 months, there was a 76% reduction in OFF-time, a reduction in daily levodopa dose of 62% and an 81% reduction in AIMS scores. These improvements suggest effects on both OFF-time and dyskinesia. However, the neuropsychological findings were less positive for STN-DBS. There was a significant worsening of the neuropsychiatric inventory (NPI) compared with baseline and at least 50% of patients exhibited apathy and other behavioural changes that were not apparent at baseline. Similar changes have been reported previously by other groups.⁴⁶

Although both apomorphine and STN-DBS produced significant clinical improvements in this study, both treatments had clear drawbacks. Apomorphine failed to treat dyskinesia and STN-DBS was associated with behavioural problems. Experience also points to additional problems with these treatments. During more than 4 years of follow-up with 50 patients receiving apomorphine, 22 have dropped out of treatment because they felt that their motor control was insufficient. In addition, patients who use longterm apomorphine (up to 16 h/day for 24 months) may develop impulse control disorders. Five patients developed such disorders, including pathological gambling, internet addiction, compulsive eating and increased libido and acute paranoia with attempted suicide. These effects are dopamine-mediated and ultimately led to treatment discontinuation.⁴³

Regarding the practicalities of administering CSAI, it is generally recommended to pre-medicate patients with the anti-dopaminergic agent domperidone 3 days prior to infusion (10 mg 3-4 times/day) in order to help suppress any potential nausea and vomiting. Patients should discontinue oral dopamine agonists. The infusion should be initiated at 1 mg/hour apomorphine whilst maintaining initially the same dose of levodopa. The dose of apomorphine should be increased by 0.5/mg/hour every 2/4 hours depending on tolerability. In order to improve dyskinesias, the dose of levodopa should be reduced on a daily basis, if possible, until complete discontinuation. If adverse events occur the infusion should be discontinued for 6-24 hours. In clinical trials, the most common reported adverse events associated with apomorphine infusion included nodules (70% incidence), sedation and somnolence (23%), nausea and vomiting (10%), renal impairment (6%), orthostatic hypotension (5%) and Coomb test positivity (6%). In addition, good local hygiene and changing the site of injection are important measures to help prevent panniculitis (a relatively rare event).

The use of apomorphine can be limited by compliance, local skin reactions at the site of injection particularly with round-the-clock administration.^{5,14,19}

As with any therapy, the selection of patients suitable to receive CSAI is of fundamental importance to optimal outcomes. Appropriate candidates include patients with idiopathic PD who have responded to levodopa and who experience motor fluctuations and/or with dyskinesias that cannot be controlled with oral therapy. Patients with cognitive impairment, advanced biological age with orthostatic hypotension, severe systemic diseases (e.g., hepatic, renal or cardiac failure), or history of dopaminergic psychosis (which is a contraindication for therapy), should be excluded. Ideally the patient should be well motivated and have available good caregiver support. Patient (and caregiver) compliance is important to ensure optimal outcomes; drop-outs for lack of compliance usually occur during the first 1-3 months of treatment.

Duodenal levodopa infusion

Constant levodopa infusion aims to achieve continuous delivery with an optimised dose that can be kept stable within the patient's individual therapeutic window. Gastric emptying must be bypassed to achieve this. A stable constant-rate intravenous infusion of levodopa (and hence stable plasma levodopa levels), first achieved in 1975, was found to ameliorate motor fluctuations in patients with PD experiencing MRC due to long-term oral levodopa.^{47,48} It was subsequently hypothesised that the development of a sustained-release formulation of levodopa would lead to improved control of the response fluctuations seen with conventional levodopa preparations. Unfortunately with current oral formulations including those that associate COMT inhibitors constant plasma levels cannot be obtained.

It was found that intravenous infusion of levodopa cannot be maintained in an individual patient for longer than 7-10 days due to poor tolerability of venous access (levodopa is irritating to veins and soft tissues) and the poor water solubility of levodopa. The subsequent development of a stable concentrated levodopa-carbidopa gel (Duodopa[®]) (levodopa/carbidopa 20/5 mg/mL in a carboxymethylcellulose mix) combined with progress in the construction and application of portable duodenal infusion systems using percutaneous endoscopic gastrostomy (PEG), facilitated the clinical use of this approach.^{49,50} The levodopa-carbidopa gel, which is administered inside the upper intestine via a small tube inserted directly into the duodenum to facilitate permanent use, has proven to be a successful therapeutic strategy.⁴⁹⁻⁵¹ It provides constant plasma levodopa levels, more continuous dopaminergic stimulation and effective treatment of motor complications through physiologic-like activation of dopamine receptors. The avoidance of low plasma levodopa trough levels has been found to reduce motor fluctuations and provide more continuous and predictable clinical benefits for patients.⁴⁹⁻⁵⁶

In clinical trials, continuous intraduodenal infusion of levodopa as monotherapy has been shown to be safe and effective with certain advantages over individually optimised combinations of conventional oral and subcutaneous medications in patients with MRC. The DIREQT (DUODOPA Infusion: Randomized efficacy and quality of life trial)⁵³ study, a randomised, controlled multicentre study involving five centres in Sweden, was the pivotal trial for use of the levodopa-carbidopa gel. Patients ($n=24$) with motor fluctuations and dyskinesia were studied in a crossover design to compare individualised, optimized, conventional treatment and levodopa-carbidopa gel for two periods of three weeks. Levodopa infusion rates averaged approximately 96 mg/hour and the average infusion time was 16.5 hours. Video scoring of motor function was assessed by blinded assessors on a global treatment response scale from -3 to 0 to +3 (severe OFF to ON to ON with severe dyskinesia). Patients also self-assessed their own

motor performance and quality of life. The primary endpoint was the percentage of ratings spent within the interval -1 to +1 (functional ON) for each treatment. Statistical analyses were performed on the intention to treat population. Overall, 21 patients received levodopa-carbidopa gel infusion and results from 20 patients were included for conventional treatment. The median rating for motor function -1 to +1 was 100% with levodopa/carbidopa duodenal infusion and 81.3% with conventional treatment ($p<0.001$). Adverse effects were generally mild and similar between the two treatment regimens. After completing the study, 16 of the enrolled patients chose to be treated with continuous daytime infusion of levodopa/carbidopa.⁵³ Our clinical experience suggests that patients appreciate the predictability of this intraduodenal infusion therapy with no medication time points to remember and find the system easy to handle.

Fluctuating motor performance is an important cause of impaired quality of life in advanced PD to which motor complications *per se* and psychosocial consequences of ON-OFF fluctuations may contribute.^{57,58} Treatment strategies that stabilize motor performance can improve the situation. In addition to demonstrating improved short- and long-term motor outcome, levodopa/carbidopa duodenal infusion may also help improve patient QoL.^{59,60} In a 12-month study of prospective clinical and quality of life changes in seven evaluable patients with PD, treatment with levodopa/carbidopa duodenal infusion was associated with significant improvements in four PDQ-39 domains (mobility, activities of daily living, stigma, bodily discomfort; $p<0.05$). Significant improvements in United Parkinson's Disease Rating Scale (UPDRS)-II (activities of daily living) and -IV (motor complications) in the "on" condition ($p<0.02$) were also observed.⁵⁹

Adverse events are generally related to the device or surgical procedure. The most frequently reported complications related to the intestinal tube included dislocation, occlusion and kink/knot in tube. Dislocation of the distal part of the tube from the duodenum into the stomach can lead to sudden deterioration of treatment response with recurring motor fluctuations. An obstruction can lead to sudden or gradual worsening of bradykinesia. Complications related to the PEG tube included loose connectors and leakage. Adverse events related to the stoma, which may cause discomfort, included secretion from the stoma, infection, proud flesh around the stoma and pain.^{53,59,60}

As it is unlikely that continuous dopaminergic infusion strategies mimic precisely the function of the dopaminergic system in the normal brain, certain cautions remain regarding their use. As they are not physiological, infusion therapies are unlikely to avoid sensitisation and tolerance. This suggests a risk that continuous delivery may also encourage the clinician to add more medications in order to extend the response to each dose of levodopa and to consider 24-hour therapy. An

unintended consequence of this may be more acute and long-term dopaminergic toxicity as a result of tolerance. However, clinical experience provides very little evidence for the development of tolerance during therapy with levodopa infusion and it is not infrequent to observe a reduction in dose needed during the first months of treatment. Despite these cautions, long-term clinical experience suggests that duodenal levodopa infusion offers an effective alternative in treating patients with advanced PD experiencing MRC.⁵³⁻⁵⁵ More importantly since levodopa is the most physiologic medication for PD theoretically any patient may benefit from infusion. In clinical practice its use is limited by costs of the product and compliance to PEG surgery.

Conclusions

Infusions provide stable plasma levels of dopaminergic medications avoiding peaks and troughs that are typical of oral administration and are the likely to contribute to the development of motor complications. Continuous dopaminergic stimulation of dopaminergic medications reduces dyskinesia and widens the therapeutic window in advanced PD. Apomorphine effect mimics levodopa is very effective in controlling off time but dyskinesia improvement is limited by the need to continue pulsatile oral levodopa therapy in the majority of the patients. However, its chronic subcutaneous infusion is limited by the occurrence of skin reactions at the site of injection and the risk of psychiatric adverse events when high doses are used.

Finally, experience with continuous duodenal levodopa infusion shows that dyskinesia and wearing-off improve considerably and benefit also involves quality of life as well as non-motor disability.

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