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NEUROLOGY AND PRECLINICAL NEUROLOGICAL STUDIES - REVIEW ARTICLE

Apomorphine and levodopa infusion for motor fluctuations and dyskinesia in advanced Parkinson disease

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Abstract
Development of motor fluctuations and dyskinesia characterizes the transition from early to advanced Parkinson disease stage. Current therapeutic strategies to manage motor complications aim at increasing the number of levodopa administrations and extending its benefit by the association of enzyme blockers and dopamine agonists. However, as disease progresses, mobility becomes progressively dependent on levodopa absorption and its plasma bioavailability, resulting in loss of independence, worse quality of life and increased caregiver burden. If patients continue to experience off-time with functional impact on activities of daily living after best medication adjustments, implementation of infusion with apomorphine or levodopa, and surgical therapies should be considered. Presence of troublesome dyskinesia would also favor the choice of an advanced treatment. Compared with pulsatile oral therapy, both apomorphine and levodopa infusion determine more continuous striatal dopamine receptors stimulation than oral levodopa resulting in significant reduction of off-time and dyskinesia, particularly peak-dose, although not in their complete resolution. This observation proves that abnormal synaptic plasticity and connectivity changes cannot be reversed once they are established. Early implementation of these therapeutic strategies ideally would target patients as soon as motor complications begin rather than at late stage of advanced Parkinson's disease (PD) before dyskinesia have manifested. Preliminary evidence from early deep brain stimulation in patients with short disease duration and modest motor complications suggests that this approach can positively impact quality of life. It is conceivable that changing our PD treatment algorithm and implementing device-aided therapies at the beginning of the advanced phase before dyskinesia has established, will provide more stable motor conditions and longer functional autonomy.

Keywords Apomorphine · Levodopa infusion gel · Duodopa · Dyskinesia · Motor complications · Wearing-off

Introduction

Effective management of Parkinson's disease (PD) requires individual customization of therapy to prevent increased motor disability and worsening quality of life (Odin et al. 2015; Antonini et al. 2018a, b). In the absence of effective disease modification, oral levodopa–carbidopa administered with or without dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and monoamine oxidase inhibitors (MAO-B) inhibitors are used for early symptom management. Advanced PD defines a stage associated with manifestation of motor and non-motor fluctuations, dyskinesia, narrowing therapeutic window, worsening quality of life and increased caregiver burden (Fox et al. 2011; Coelho and Ferreira 2012). At this stage, motor deficits during off-periods aggravate and the on-phase is frequently complicated by dyskinesia (Bjornestad et al. 2016). Management of advanced PD (APD) symptoms, particularly motor fluctuations, wearing-off and dyskinesia requires optimization of oral therapies (including polypharmacy, dose fractioning and dose tapering) (Antonini et al. 2010).

Since levodopa has a short plasma half-life time, fractionating levodopa intake several times during the day may improve wearing-off, but does not modify its concentration in the blood. Depending on age and dose, pulsatile levodopa delivery along with progressive loss of striatal dopamine nerve terminals heralds the development of wearing-off and dyskinesia (Antonini et al. 2018a, b; Bellucci et al. 2017). In general, use of levodopa doses higher than 600 mg/day

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or more then 5–6 mg/kg body weight, has been associated with significant risk of motor complication 3–5 years after treatment initiation (Fahn et al. 2004; Sharma et al. 2008).

Beside shortening the time between doses and increasing the number of levodopa intakes, other strategies have proven effective in managing wearing-off, including use of COMT and MAO-B enzyme blockers to extend levodopa and dopamine half-life. They have complementary effects since COMT inhibitors extend peripheral levodopa half-life while MAO-B blockers reduce striatal dopamine clearance.

Unlike off-periods, appearance of dyskinesia is related to the development of long-term plastic changes in striatal neurons leading to abnormal signal transmission and connectivity (Calabresi et al. 2010; Carta and Bezard 2011; Bezard 2013; Porras et al. 2014; Cenci and Crossman 2018). Moreover, patients are frequently unaware of their presence particularly in the early phase (Pilleri and Antonini 2015).

Amantadine, a NMDA receptor antagonist is well known for its efficacy to treat slight-to-moderate dyskinesia and motor complications. Its use has been further evaluated in a new extend release formulation that was recently introduced to market with the expectation of better tolerability (Elkurd et al. 2018).

APD may be accompanied in the late stage by additional motor and non-motor symptoms which may only marginally benefit from treatment including, postural instability leading to frequent falls with increased risk of fractures, sleep disturbances, hallucinations/psychosis, delusions, cognitive dysfunction and dementia. Therefore, definition of appropriate therapeutic strategy will require thorough multidisciplinary assessment and evaluation (Fabbri et al. 2017).

In most cases persistence of fluctuating motor disability requires consideration for device-aided therapies such as deep brain stimulation (DBS), continuous subcutaneous apomorphine (CSAI) or levodopa–carbidopa intestinal gel (LCIG) infusion (Antonini and Tolosa 2009; Timpka et al. 2017; Antonini et al. 2018a, b). Gaps in clinical knowledge exist in defining timing of initiation of these treatments and assessing which therapies are most effective (Fox et al. 2011).

Recently, following the publication of the EARLY-STIM trial, the FDA expanded the approved use of deep brain stimulation (DBS) in PD to include patients and who had only 4 years disease durations and recently developed motor complications (Schuepbach et al. 2013; Dafsari et al. 2017). This indication revision essentially makes this therapy available at an early time-point in PD at the early phase of APD and opens to changes in our current treatment algorithm including timing of infusion therapies (Cabrera et al. 2018).

Infusion therapies

Infusion therapies have progressively established as the most effective pharmacological strategies to manage motor complications in advanced patients.

In the earlier stages of the disease, oscillations in levodopa plasma levels are not clearly associated with fluctuations in motor function, presumably due to central 'buffering' via intraneuronal storage in surviving nigrostriatal terminals, providing continuous stimulation even in the context of discontinuous exogenous delivery.

The issue of continuous drug delivery is also relevant to the current understanding of mechanisms underlying the development of levodopa-induced dyskinesia. In animal models of PD, administration of D1 or D2 agonists with short half-lives is associated with dyskinetic responses (Maratos et al. 2003) while exposure to long-acting agonists does not induce dyskinesia (Hadj Tahar et al. 2000). The same differences have also been observed in studies comparing pulsatile versus continuous delivery of the same dopaminergic agent. These results are consistent with clinical studies of continuous infusions of DAs, including lisuride, which were found to downregulate pre-existing LD-induced dyskinesia (Stocchi et al. 2002).

Although pulsatile stimulation may not be sufficient to explain the mechanisms underlying the induction of dyskinesia, such observations highlight the need to optimize dopaminergic delivery in PD. Current oral extended-release or transdermally delivered agonists cannot provide sufficient efficacy to ensure monotherapy. Several attempts to improve levodopa oral administration have included the development of sustained-release preparations. Unfortunately, randomized controlled studies have failed to reveal differences between such formulations and standard levodopa with respect to long-term dyskinesia risk (Antonini et al. 2010).

Apomorphine subcutaneous infusion and acute injection

Subcutaneous administration of apomorphine ensures rapid efficacy, and has proven to be particularly suitable for acute and continuous delivery through pump systems.

Acute injections are highly effective, but largely underused due to the difficulty in self-administration in presence of severe disability during the off period. By contrast, effects on motor fluctuations with daily subcutaneous infusion are well established (Jenner and Katzenschlager 2016a, b). All studies are consistently showing both reduction of off-time and extension of on-time as well as

improved off-related disability. The effect on dyskinesia is more variable and depends on the possibility to increase apomorphine infusion rate and significantly reduce the dose of concomitant levodopa (Borgemeester et al. 2016; Sesar et al. 2017). Non-motor symptoms were shown to improve significantly and benefit on depression and more recently in impulse control disorders has been reported in some patients (Antonini et al. 2011; Martinez-Martin et al. 2015). More recently, large open-label studies have demonstrated a significant improvement in quality of life after long-term use (Drapier et al. 2016).

The superiority of apomorphine vs. placebo was recently tested in the randomized double-blind TOLEDO study (Katzenschlager et al. 2018). The infusion dose was individually optimized between 3 and 8 mg/h and administered for 16 ± 2 h of their waking day. The study demonstrated efficacy of continuous subcutaneous infusion in providing a significant and clinically meaningful reduction in 'off' time of approximately 2 h more than placebo and equal extension of on-time without troublesome dyskinesia (Fig. 1).

The study also confirmed well-known reported complications, particularly skin nodules at infusion site that were present in 44% of treated patients followed by nausea somnolence and skin erythema.

Infusion of levodopa–carbidopa intestinal gel (LCIG)

Since its initial development in 1991 as liquid solution, levodopa infusion has undergone extensive research to reduce injected volume and make it more stable for commercial use, eventually proving its safety and efficacy for APD treatment in the current LCIG formulation (Antonini et al. 2013; Wirdefeldt et al. 2016).

The superiority of LCIG vs. best oral medical treatment in reducing off-time and extending on-time has been proven in a double-blind, double-dummy trial (Olanow et al. 2014). At the end of 12 weeks observation decrease in 'off' time and increase in 'on' time without troublesome dyskinesia favored LCIG by −1.91 and +1.86, respectively. Overall, the study showed that motor changes were associated with better quality of life and reduced caregiver burden, although a significant number of subjects experienced procedure-related complications, particularly in the first week of treatment (Fig. 1).

Dyskinesia is difficult to treat in the advanced stage of PD as it becomes more prominent with long-term oral levodopa replacement therapy. At this stage in disease, the "on" time of motor fluctuations and dyskinesia have previously been correlated with high levels of levodopa in the plasma or cerebrospinal fluid. LCIG provides a continuous exposure to levodopa during waking hours (16 h) and has the potential to circumvent complications such as dyskinesia by attenuating peak levodopa levels. Both open-label and randomized double-blind studies showed a reduction in time with troublesome dyskinesia following LCIG confirming benefit from pharmacokinetic optimization (Antonini et al. 2016).

These results were further strengthened by open-label observations including long-term results of the GLORIA study where motor and non-motor benefits were reported in more than 250 patients followed for 2 years (Antonini et al. 2017).

However, both results from the pivotal study as form long-term open-label GLORIA registry study showed that while improved in severity and duration motor complications and in particular dyskinesia continue to occur suggesting

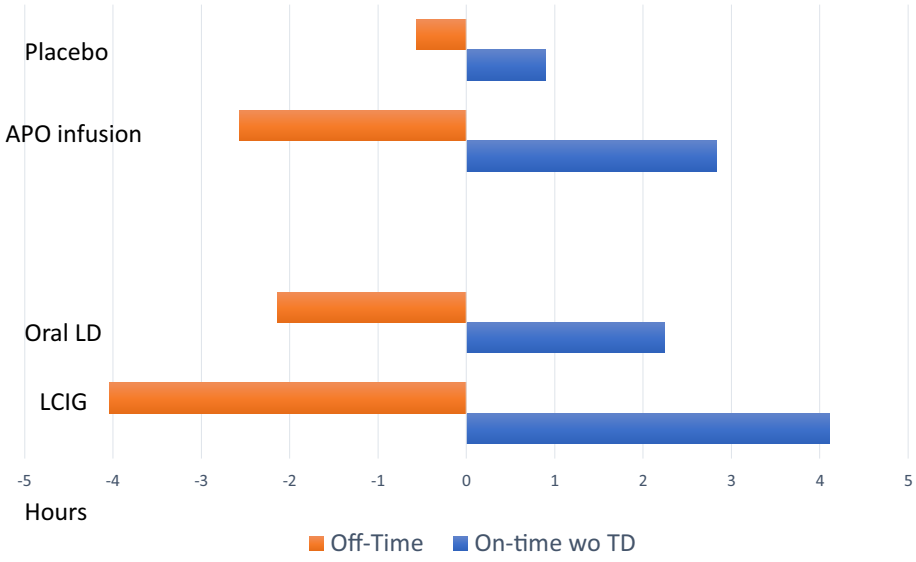

Fig. 1 Efficacy of extension of on-time without troublesome dyskinesia and reduction of off-time from the LCIG and apomorphine (Toledo) randomized double-blind studies

persistence of abnormal post-synaptic pharmacodynamic response to levodopa administration.

Some concerns have been raised by the observation of polyneuropathy in patients with LCIG. These reports have showed two general profiles of polyneuropathy in LCIG patients: a less severe sensory axonal subtype that is slowly progressive, and a less common subtype that clinically resembles acute inflammatory polyneuropathy (Guillain–Barré like syndrome) and causes severe deficits. However, overall incidence is hardly estimated from these reports although recently published observations report it around 5% of treated patients (Lang et al. 2016; Sensi et al. 2017).

Conclusion

Advanced PD raises multiple management issues, as the patient carries the burden of the motor complications making medication adjustments quite complex. Adequate control and optimal quality of life are often difficult to achieve and an integrated understanding of the pathophysiological mechanisms underlying the symptoms and of the multiple drug interactions is mandatory.

This is particularly true for dyskinesia that can be reduced but not fully controlled with advanced therapies. Preliminary results in patients with troublesome dyskinesia switched from oral to infusion therapy have demonstrated that even if a significant improvement can be achieved both in severity and duration, they are not completely abolished (Antonini et al. 2016; Timpka et al. 2016; Katzenschlager et al. 2005). Similarly, management of dyskinesia in patients treated with DBS of the subthalamic nucleus requires reduction of concomitant levodopa therapy (Schuepbach et al. 2013; Vizcarra et al. 2018).

This evidence supports the concept of priming for levodopa-induced dyskinesia well established by animal models with some differences in humans related to aging and extent of nigrostriatal system denervation (Calabresi et al. 2010).

Therefore, specific indicators for screening and monitoring of efficacy particularly in the decision to move from conventional therapies to more invasive treatments are warranted. Experience and familiarity of the team with specific procedures is important, but novel outcome measures based on quality of life and activities of daily living improvement, maybe using wearable technologies, should be soon implemented. The final objective would be to possibly start these treatments as soon as motor complications develop. However, this will require more data on long-term safety and full cost–benefit analysis.

Compliance with ethical standards

Conflict of interest Authors declare no competing interest.

References

Antonini A, Tolosa E (2009) Apomorphine and levodopa infusion therapies for advanced Parkinson's disease: selection criteria and patient management. Expert Rev Neurother 9:859–867

Antonini A, Chaudhuri KR, Martinez-Martin P, Odin P (2010) Oral and infusion levodopa-based strategies for managing motor complications in patients with Parkinson's disease. CNS Drugs 24:119–129

Antonini A, Isaias IU, Rodolfi G et al (2011) A 5-year prospective assessment of advanced Parkinson disease patients treated with subcutaneous apomorphine infusion or deep brain stimulation. J Neurol 258:579–585

Antonini A, Odin P, Lopiano L et al (2013) Effect and safety of duodenal levodopa infusion in advanced Parkinson's disease: a retrospective multicenter outcome assessment in patient routine care. J Neural Transm 120:1553–1558

Antonini A, Fung VS, Boyd JT et al (2016) Effect of levodopa-carbidopa intestinal gel on dyskinesia in advanced Parkinson's disease patients. Mov Disord 31:530–537

Antonini A, Poewe W, Chaudhuri KR, GLORIA Study Co-investigators et al (2017) Levodopa-carbidopa intestinal gel in advanced Parkinson's: final results of the GLORIA registry. Parkinsonism Relat Disord 45:13–20

Antonini A, Moro E, Godeiro C, Reichmann H (2018a) Medical and surgical management of advanced Parkinson's disease. Mov Disord. https://doi.org/10.1002/mds.27340

Antonini A, Robieson WZ, Bergmann L, Yegin A, Poewe W (2018b) Age/disease duration influence on activities of daily living and quality of life after levodopa-carbidopa intestinal gel in Parkinson's disease. Neurodegener Dis Manag 8:161–170

Bellucci A, Antonini A, Pizzi M, Spano P (2017) The end is the beginning: Parkinson's disease in the light of brain imaging. Front Aging Neurosci 9:330. https://doi.org/10.3389/fnagi.2017.00330

Bezard E (2013) Experimental reappraisal of continuous dopaminergic stimulation against L-dopa-induced dyskinesia. Mov Disord 28:1021–1022

Bjornestad A, Forsaa EB, Pedersen KF, Tysnes OB, Larsen JP, Alves G (2016) Risk and course of major complications in a population-based incident Parkinson's disease cohort. Park Relat Disord 22:48–53

Borgemeester RW, Drent M, van Laar T (2016) Motor and non-motor outcomes of continuous apomorphine infusion in 125 Parkinson's disease patients. Park Relat Disord 23:17–22

Cabrera LY, Goudreau J, Sidiropoulos C (2018) Critical appraisal of the recent US FDA approval for earlier DBS intervention. Neurology. https://doi.org/10.1212/WNL.0000000000005829

Calabresi P, Di Filippo M, Ghiglieri V, Tambasco N, Picconi B (2010) Levodopa-induced dyskinesias in patients with Parkinson's disease: filling the bench-to-bedside gap. Lancet Neurol 9(11):1106–1117

Carta M, Bezard E (2011) Contribution of pre-synaptic mechanisms to L-DOPA-induced dyskinesia. Neuroscience 198:245–251

Cenci MA, Crossman AR (2018) Animal models of l-dopa-induced dyskinesia in Parkinson's disease. Mov Disord. https://doi.org/10.1002/mds.27337

Coelho M, Ferreira JJ (2012) Late-stage Parkinson disease. Nat Rev Neurol 8:435–442

Dafsari HS, Reker P, Silverdale M et al (2017) Subthalamic stimulation improves quality of life of patients aged 61 years or older with short duration of Parkinson's disease. Neuromodulation. https://doi.org/10.1111/ner.12740

Drapier S, Eusebio A, Degos B et al (2016) Quality of life in Parkinson's disease improved by apomorphine pump: the OPTIPUMP cohort study. J Neurol 263:1111–1119

Elkurd MT, Bahroo LB, Pahwa R (2018) The role of extended-release amantadine for the treatment of dyskinesia in Parkinson's disease patients. Neurodegener Dis Manag

Fabbri M, Coelho M, Guedes LC et al (2017) Response of non-motor symptoms to levodopa in late-stage Parkinson's disease: results of a levodopa challenge test. Parkinsonism Relat Disord 39:37–43

Fahn S, Oakes D, Shdoulson I et al (2004) Levodopa and the progression of Parkinson's disease. N Engl J Med 351:2498–2508

Fox SH, Katzenschlager R, Lim SY et al (2011) The movement disorder society evidence-based medicine review update: treatments for the motor symptoms of Parkinson's disease. Mov Disord 26(Suppl 3):S2–S41

Hadj Tahar A, Gregoire L, Bangassoro E, Bedard PJ (2000) Sustained cabergoline treatment reverses levodopa-induced dyskinesias in parkinsonian monkeys. Clin Neuropharmacol 23:195–202

Jenner P, Katzenschlager R (2016a) Apomorphine—pharmacological properties and clinical trials in Parkinson's disease. Parkinsonism Relat Disord 33(Suppl 1):S13–S21

Jenner P, Katzenschlager R (2016b) Apomorphine—pharmacological properties and clinical trials in Parkinson's disease. Park Relat Disord 33(Suppl 1):S13–S21

Katzenschlager R, Hughes A, Evans A et al (2005) Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson's disease: a prospective study using single-dose challenges. Mov Disord 20:151–157

Katzenschlager R, Poewe W, Rascol O et al (2018) Double-blind, randomised, placebo-controlled, phase III study (Toledo) to evaluate the efficacy of apomorphine subcutaneous infusion in reducing 'off' time in Parkinson's disease patients with motor fluctuations not well controlled on optimised medical treatment. Lancet Neurol **(in press)**

Lang AE, Rodriguez RL, Boyd JT et al (2016) Integrated safety of levodopa-carbidopa intestinal gel from prospective clinical trials. Mov Disord 31:538–546

Maratos EC, Jackson MJ, Pearce RK, Cannizzaro C, Jenner P (2003) Both short- and long-acting D-1/D-2 dopamine agonists induce less dyskinesia than L-DOPA in the MPTP-lesioned common marmoset (Marmoset/*Callithrix jacchus*). Exp Neurol 179:90–102

Martinez-Martin P, Reddy P, Katzenschlager R et al (2015) EuroInf: a multicenter comparative observational study of apomorphine and levodopa infusion in Parkinson's disease. Mov Disord 30:510–516

Odin P, Ray Chaudhuri K, Slevin JT, National Steering Committees et al (2015) Collective physician perspectives on non-oral medication approaches for the management of clinically relevant unresolved issues in Parkinson's disease: consensus from an international survey and discussion program. Parkinsonism Relat Disord 21:1133–1144

Olanow CW, Kieburtz K, Odin P et al (2014) Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: a randomised, controlled, double-blind, double-dummy study. Lancet Neurol 13:141–149

Pilleri M, Antonini A (2015) Therapeutic strategies to prevent and manage dyskinesias in Parkinson's disease. Expert Opin Drug Saf 14:281–294

Porras G, De Deurwaerdere P, Li Q, Marti M, Morgenstern R, Sohr R, Bezard E, Morari M, Meissner WG (2014) L-Dopa-induced dyskinesia: beyond an excessive dopamine tone in the striatum. Sci Rep 4:3730

Schuepbach WM, Rau J, Knudsen K et al (2013) Neurostimulation for Parkinson's disease with early motor complications. N Engl J Med 368:610–622

Sensi M, Cossu G, Mancini F et al (2017) Which patients discontinue? Issues on Levodopa/carbidopa intestinal gel treatment: Italian multicentre survey of 905 patients with long-term follow-up. Parkinsonism Relat Disord 38:90–92

Sesar Á, Fernández-Pajarín G, Ares B, Rivas MT, Castro A (2017) Continuous subcutaneous apomorphine infusion in advanced Parkinson's disease: 10-year experience with 230 patients. J Neurol 264:946–954

Sharma JC, Ross IN, Rascol O, Brooks D (2008) Relationship between weight, levodopa and dyskinesia: the significance of levodopa dose per kilogram body weight. Eur J Neurol 15:493–496

Stocchi F, Ruggieri S, Vacca L, Olanow CW (2002) Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 125:2058–2066

Timpka J, Fox T, Fox K, Honig H, Odin P, Martinez-Martin P, Antonini A, Chaudhuri KR (2016) Improvement of dyskinesias with L-dopa infusion in advanced Parkinson's disease. Acta Neurol Scand 133:451–458

Timpka J, Nitu B, Datieva V, Odin P, Antonini A (2017) Device-aided treatment strategies in advanced Parkinson's disease. Int Rev Neurobiol 132:453–474

Vizcarra JA, Situ-Kcomt M, Artusi CA et al (2018) Subthalamic deep brain stimulation and levodopa in Parkinson's disease: a meta-analysis of combined effects. J Neurol. https://doi.org/10.1007/s00415-018-8936-2

Wirdefeldt K, Odin P, Nyholm D (2016) Levodopa-carbidopa intestinal gel in patients with Parkinson's disease: a systematic review. CNS Drugs 30:381–404