Dopamine Agonist Therapy in Advanced Parkinson’s Disease

Heinz Reichmann
Department of Neurology,
University of Dresden,
Dresden, Germany

Introduction

“Parkinson’s disease (PD) doesn’t kill you, it takes your life away.” This is a disturbing quotation by the English Parkinson Lay Organisation. There is, however, no other neurodegenerative disease which responds better to treatment than PD. Treatment of advanced PD is located between these poles (Figure 1). Most national guidelines and papers on the treatment of PD recommended that early phases are treated with dopamine agonists and monoamine oxidase B inhibitors and late phases with levo-dopa. Common guidelines and publications regarding the treatment of late phase PD have thus not yet focused on dopamine agonists. This appears somewhat surprising because nowadays most patients commence treatment with a dopamine agonist. Strategic management of PD has to take into consideration the following points: 1) many patients will receive therapy for 15-20 years, 2) PD should be managed optimally throughout its course, 3) the aim of strategic management is to maintain efficacy and minimize side-effects in both the short and long term, and 4) initial therapy should be sustained for the long-term therapy. These criteria demand that treatment is initiated with efficacious and safe drugs and dopamine agonists meet this request.

The main reason for their use is, however, that due to its short plasma half-life, levo-dopa induces dyskinesia. Conversely, dopamine agonists have longer half-lives and therefore stimulate dopamine receptors in a more tonic, continuous way, thus avoiding or at least decreasing the occurrence and severity of dyskinesia.1 It is for fear of the risk of developing side effects such as hallucinations, psychosis, orthostatic hypotension, nausea and vomiting that dopamine agonists are not normally used in advanced stages, rather than their loss of efficacy. For this reason, it would be most helpful to have measures to identify those patients with a high tolerance of dopamine agonists, in order to either allow them to continue with dopamine agonist therapy for as long as possible, or to add dopamine agonists in advanced stages.

This review will briefly consider these options and will conclude that it may be beneficial to use modern dopamine agonists such as ropinirole slow release (Modutab®) or the rotigotine patch, even in the elderly or in advanced PD patients.

The Concept of Continuous Dopamine Replacement Therapy

Most patients with advanced PD receive levo-dopa or levo-dopa combined with a catechol-O-methyl transferase (COMT) inhibitor.23 Whilst this treatment reduces the risk of developing dyskinesia, it still does not appear to be as effective as a dopamine agonist with a long plasma half-life. Meanwhile, it has been shown that even taking multiple doses of a levo-dopa/COMT inhibitor preparation per day still results in peaks and troughs of levo-dopa blood levels and induces dyskinesia. Only the continuous supply of levo-dopa via the so-called “DuoDopa pump” is able to diminish the dyskinesia rate and to increase the number of “on” phases (Figure 2).4

Analyses of the levo-dopa levels in the blood of such patients show a very constant concentration with less peaks and troughs, which is reflected by the low dyskinesia rate.5 This indicates that it is not the drug (levo-dopa) per se which causes dyskinesia, but rather its
pharmacokinetics: when levo-dopa is supplied continuously, it is as good as dopamine agonists in preventing patients from becoming dyskinetic.

**Dopamine Agonists in Advanced Parkinson's Disease Patients**

A perfect example of a pump therapy for PD is the apomorphine pump (Figure 3).6,7 Apomorphine has a plasma half-life of about twenty minutes, which is the shortest half-life of all dopamine agonists, however, if continuously delivered via a pumping system, apomorphine is highly potent in patients with advanced PD, and suppresses dyskinesia. Unfortunately, the subcutaneous application of the drug leads to serious skin irritation (panniculitis) in some patients, and some patients develop hallucinations, both serious side effects which lead to most patients stopping this treatment after two years. Thus, both the DuoDopa pump and the apomorphine pump are invasive methods which are associated with several problems.

This is why deep brain stimulation is the most highly recommended and most often used therapy in the treatment of dyskinetic and advanced PD patients.8,9 Deep brain stimulation is achieved via electrodes which are inserted into both thalamic nuclei. Most patients achieve a considerable improvement in mobility and a decrease in dyskinesias. Again, this is an invasive and risky method which also involves brain surgery. Thus, an oral medication which is as potent as these invasive measures and also safe would be desirable.

It has already been outlined that dopamine agonists have a longer plasma half-life than levo-dopa. At the moment, cabergoline is the dopamine agonist with the longest plasma half-life (68 hours).10 Another important advantage of cabergoline is its once-a-day use, which results in very good compliance. In line with this, there are several reports which show that too high a fractionation of any medication, including anti-PD medication, leads to poor patient compliance.11 Unfortunately, due to the associated risk of heart valve fibrosis,12 cabergoline, together with pergolide, is now restricted to second line use. Aside from this serious drawback, cabergoline has proven to be associated with a low occurrence of dyskinesia and guarantees good mobility at night as well as during the day, which results in improved sleep. The first alternative to orally administered cabergoline was, at least in some countries, the dopamine agonist rotigotine, which is a

---

**Figure 1.** Limitations of multiple dosing for Parkinson's disease. It is common practice to initiate dosing of L-dopa two or three times daily, however adjustments in dose level and dose frequency are often needed to maintain symptomatic control as the disease progresses. It is not uncommon for L-dopa to be dosed four or more times daily. Furthermore, frequent doses do not address the pulsatile delivery of L-dopa: there are still large fluctuations in plasma drug levels.

**Figure 2.** DuoDopa pump. DuoDopa is a combination of levo-dopa and carbidopa in the form of a gel that is administered directly into the small intestine through a surgically placed tube for advanced Parkinson's disease. It can help maintain a constant plasma concentration of levodopa and reduce off time and incidence of dyskinesia.

**Figure 3.** Apomorphine pump. Apomorphine is the shortest half-life of all dopamine agonists, however, if continuously delivered via a pumping system, apomorphine is highly potent in patients with advanced PD, and suppresses dyskinesia. PD: Parkinson's disease.
non-ergot derivative and thus does not cause valvulopathy. Rotigotine is applied via a patch once daily (Figure 4). There are several convincing studies showing that the rotigotine patch not only guarantees continuous delivery of the drug, but is also highly efficacious. Side effects are similar to those found with oral non-ergot dopamine agonists such as ropinirole, pramipexole or piribendil. Rotigotine treatment resulted in statistically significant improvements in “off”-time, of responder rates, and an increase in “on”-time when compared to placebo in patients with advanced PD. In the so-called CLEOPATRA trial, non-inferiority of rotigotine to ropinirole was shown for reduction in “off”-time. Rotigotine was safe and well tolerated. Except for skin reaction at the site of application, the rate of adverse events was comparable for the pramipexole and rotigotine group.

A new preparation of ropinirole was recently licensed. This slow-release preparation is administered in tablet form once daily, and plasma concentrations of the drug only decrease steeply shortly after intake, causing the above mentioned side effects. In contrast, the plasma levels of ordinary dopamine agonists in-crease steeply shortly after intake, causing the above mentioned side effects. Thus, it is the new formulation of dopamine agonists which permits their use in advanced stages of PD. Within the next two years, an increasing number of long-acting dopamine agonists will become available. A lisuride patch and an ER formulation of pramipexole will both be available.

REFERENCES
1. Rascol O, Brooks DJ, Koczyw AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson’s disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000;342:1481-1491.
2. Baas H, Beiske AG, Ghika J, Jackson M, Oertel W, Poeoe W, et al. Catechol-O-methyltransferase inhibition with tolcapone reduces the “wearing off” phenomenon and levodopa requirements in fluctuating parkinsonian patients. J Neurol Neurosurg Psychiatry 1997;63:421-428.
3. Smith LA, Jackson MJ, Al-Barghouthy G, Rose S, Kaoumpamaki M, Olanow W, et al. Multiple small doses of levodopa plus entacapone produce continuous dopaminergic stimulation and reduce dyskinesia induction in MPTP-treated drug-naive primates. Mov Disord 2005;20:306-314.
4. Nyholm D, Nilsson Renmal Al, Dizard N, Constantinescu R, Holmberg B, Jansson R, et al. Duodenal levodopa infusion monotherapy versus oral polypharmacy in advanced Parkinson disease. Neurology 2005;64:216-223.
5. Stocchi F, Vaccia L, Ruggieri S, Olanow CW. Intermittent vs continuous levodopa administration in patients with advanced Parkinson disease: a clinical and pharmacokinetic study. Arch Neurol 2005;62:905-910.
6. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson’s disease. J Neurol Neurosurg Psychiatry 1998;64:573-576.
7. Katzenschlager R, Hughes A, Evans A, Manson AJ, Hoffman M, Swinn L, et al. Continuous subcutaneous apomorphine therapy improves dyskinesias in Parkinson’s disease: a prospective study using single-dose challenges. Mov Disord 2005;20:151-157.
8. Deuschl G, Schade-Brittinger C, Kraack P, Volkmarne J, Schaller H, Bötzel K, et al. A randomized trial of deep-brain stimulation for Parkinson’s disease. N Engl J Med 2006;355:896-908.
9. Kleiner-Fisman G, Herzog J, Fisman DN, Tamma F, Lyons KE, Pahwa R, et al. Subthalamic nucleus deep brain stimulation: summary and meta-analysis of outcomes. Mov Disord 2006; Suppl 14:S290-304.
10. Rimke UK, Bracco F, Chouza C, Dupont E, Gershunick O, Marti Masso JF, et al. Early treatment of Parkinson’s disease with cabergoline delays
the onset of motor complications. Results of a double-blind levodopa controlled trial. The pkds009 Study Group. Drugs 1998;55(Suppl 1): 23-30.
11. Grosset D, Antonini A, Canesi M, Pezzoli G, Lees A, Swaw K, et al. Adherence to antiparkinson medication in a multicenter European study. Mov Disord 2009 Feb 3.
12. Yamamoto M, Uesugi T, Nakayama T. Dopamine agonists and cardiac valvulopathy in Parkinson disease: a case-control study. Neurology 2006;67:1225-1229.
13. Watts RL, Jankovic J, Waters C, Rajput A, Boroojerdi B, Rao J. Randomized, blind, controlled trial of transdermal rotigotine in early Parkinson disease. Neurology 2007;68:272-276.
14. Poewe WH, Rascol O, Quinn N, Tolosa E, Oertel WH, Martignoni E, et al: SP 515 Investigators. Efficacy of pramipexole and transdermal rotigotine in advanced Parkinson’s disease: a double-blind, double-dummy, randomised controlled trial. Lancet Neurol 2007;6:513-520.
15. Tompson DJ, Vearer D. Steady-state pharmacokinetic properties of a 24-hour prolonged-release formulation of ropinirole: results of two randomized studies in patients with Parkinson’s disease. Clin Ther 2007;29:2654-2666.
16. Pahwa R, Stacy MA, Factor SA, Lyons KE, Stocchi F, Hersh BP, et al: EASE-PD Adjunct Study Investigators. Ropinirole 24-hour prolonged release: randomized, controlled study in advanced Parkinson disease. Neurology 2007;68:1108-1115.