Psychiatria Danubina, 2011; Vol. 23, No. 1, pp 80–83 *Conference paper*

MYTHS AND REALITIES OF CONTINUOUS DOPAMINERGIC STIMULATION

Zvezdan Pirtošek

Department of Neurology, University Medical centre, Ljubljana, Slovenia

SUMMARY

Motor fluctuations and dyskinesia in later stages of Parkinson's disease (PD) are caused by pharmacokinetic as well as pharmacodynamic factors, intermittent dopaminergic stimulation being one of the most important. In the healthy brain, dopamine neurons in the substantia nigra pars compacta fire tonically at a steady rate of about 4 cycles/second. In later stages of PD, steady firing is replaced by pulsatile stimulation which causes molecular and physiologic changes in the basal ganglia. Continuous dopaminergic stimulation has been shown to dramatically improve motor fluctuations and dyskinesia by modifications of oral treatment (dopamine agonists, smaller, more frequent levodopa doses, controlled-release formulation of levodopa, addition of agents that slow down the catabolism of dopamine, such as inhibitors of catechol-O-methyl transferase and monoamine oxidase), transdermal delivery (rotigotine), infusion therapies (intravenous levodopa, subcutaneous application of apomorphine and lisuride, duodenal infusion of levodopa) and deep brain stimulation of the subthalamic nucleus.

Key words: *Parkinson's disease - continuous dopaminergic stimulation – levodopa - neuronal firing - basal ganglia*

* * * * *

INTRODUCTION

Pathophysiology of Parkinson's disease involves loss of nigral dopaminergic neurons. Clinically significant striatal dopaminergic deficiency leads to characteristic motor clinical hallmarks including bradykinesia, hypokinesia, rigidity, tremor, and loss of postural reflexes. Levodopa, dopamine precursor, remains the gold standard for the relief of these symptoms. However, after a few years of therapy with levodopa the response to oral dopaminergic drugs becomes unstable. Motor fluctuations and dyskinesia emerge and often represent a major source of disability for PD patients.

In this article we will introduce the concept of continuous dopaminergic stimulation (CDS), review mechanisms by which levodopa causes motor fluctuations and dyskinesia and describe what goes wrong with neuronal firing after years of intermittent levodopa treatment. The rationale of CDS, various ways to achieve a more stable levodopa plasma level and realities and myths of CDS are described.

Mechanisms of levodopa-induced motor fluctuations and dyskinesia

Unstable response in later stages of Parkinson's disease to levodopa is caused by pharmacokinetic as well as pharmacodynamic factors (Verhagen 1999).

1. peripheral pharmacokinetic factors:
   - short plasma half-life of L- dopa of around 90 minutes;
   - erratic gastric emptying and consequent erratic absorption of levodopa in the duodenum;
   - variations in gastric acidity;
   - competition of levodopa with other dietary large neutral amino acids for entry across the duodenal wall and across the blood-brain barrier;
   - Helicobacter pylori infection;
   - dissipation by unwanted decarboxylation in the gut, liver, and extracerebral capillaries (reduced by the concurrent routine use of peripheral dopa decarboxylase inhibitors).

Peripheral factors can be bypassed by parenteral administration.

2. central pharmacodynamic factors:
   - severe nigrostriatal denervation in later stages of Parkinson' disease: loss of dopamine in the pars compacta of the substantia nigra decreases striatal concentration of dopamine and makes it more dependent on the plasma levels of levodopa;
   - long-term intermittent levodopa administration (see below).

Apart from pharmacokinetic and pharmacodynamic factors, levodopa dosage, disease duration, severity of motor symptoms and age represent the risk factors for the occurrence of motor fluctuations and dyskinesia, with higher doses, longer disease duration, more severe motor symptoms and younger patient having higher risk to develop early and severe complications. Continuous dopaminergic stimulation has been shown to dramatically improve motor fluctuations and dyskinesia. Continuous dopaminergic stimulation is a therapeutic strategy for the management of Parkinson's disease, which proposes that dopaminergic agents that provide continuous stimulation of striatal dopamine receptors will ameliorate, delay or prevent the onset of levodopa-related motor complications.

Firing of dopaminergic neurons in health and disease

In the healthy brain, dopamine neurons in the substantia nigra pars compacta fire tonically at a steady

rate of about 4 cycles/second. This background steady firing results in stable levels of dopamine in the striatum which is maintained across the range of motor programmes in the resting as well as in the moving conditions of the organism (Skirboll et al. 1990, Sarre et al. 1994). Only when animal anticipates the reward (e.g. food) or when a novel stimulus occurs in the environment, dopamine nigrostriatal neurons start firing in bursts (Schultz 1994), modifying the extracellular content of dopamine for minutes or hours; afferent inputs from the cortical areas can also induce slower or more tonic release of dopamine (Inoue et al. 2004). But in all these instances the intrasynaptic dopamine levels in the striatum remain steady because the dopamine reuptake capability of dopamine transporter and the autoregulatory mechanisms of dopaminergic neurons remain efficient. This is important because the basal ganglia function, related to movement and selection of automatic programmes must be stable and predictable; it is dopamine and its stable level in the striatum which enables these functions to run smoothly.

In later stages of Parkinson's disease, as the number of dopamine-producing nigral neurons decrease from ~50% at symptom onset to ≤20%, the buffering capacity of the brain is lost and dopamine can no longer be released tonically. Steady firing is replaced by pulsatile stimulation which causes molecular and physiologic changes in the basal ganglia:

- transmitter modifications cause long term potentiation of the synaptic efficacy of glutamate receptors of the N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4 isoxazolepropionic acid (AMPA) subtype on medium spiny neurons. These neurons become more sensitive to excitation by cortical glutamatergic projections;
- modifications of gene and protein expression, including enkephalin, dynorphin, neurotensin, Fos and JunB proteins, ERK1/DARP32 and D1 signalling molecules (Calon et al. 2000).

These modifications in the striatum induce remodelling of neuronal contacts and pathways and thus impair the capability of selecting and facilitating normal movement. The patient develops motor fluctuations and dyskinesia.

Therapeutic implications

Delivering dopaminergic therapies in a more continuous and physiologic manner has proved to be an excellent treatment in advanced PD patients, but it may be also beneficial in de novo patients. In an early stage continuous stimulation of striatal dopamine receptors may delay or prevent priming for motor fluctuations and dyskinesia which are so characteristic for the advanced PD and caused (also) by non-continuous, pulsatile stimulation of dopamine. Levodopa-related motor complications include motor fluctuations (wearing-off phenomena, end-of-dose hypokinesia, early-morning hypokinesia, postprandial hypokinesia, nocturnal hypokinesia, unpredictable on-off fluctuations) and dyskinesia (interdose, onset, end of dose, and off period). A more continuous stimulation may reverse the development of such complications, enabling the patient to achieve markedly improved quality of life.

Studies in primate models and patients with Parkinson's disease have shown that problems posed by long-term treatment with levodopa can be circumvented by several ways which have been developed to reduce existing motor response fluctuations and delay the emergence of the future ones.

(i) Modifications of oral treatment

a. (addition of) dopamine agonists: These agents directly stimulate the dopamine receptors and have mostly longer half-life, but are much less efficient compared to levodopa, with more psychiatric side effects. Dopamine agonists with longer half-life induce a significant delay in the onset of motor complications, both dyskinesias and fluctuations (The Parkinson Study Group 2004). Short-acting dopamine agonist like apomorphine rapidly induces dyskinesia if injected as bolus, but not if delivered as continuous infusion (Bibbiani et al., 2005);
b. smaller, more frequent levodopa doses
c. controlled-release formulation of levodopa
d. addition of agents that slow down the catabolism of the active derivative dopamine, such as inhibitors of catechol-O-methyl transferase (COMT) and monoamine oxidase (MAO).

COMT is the catabolic enzyme that converts levodopa into its main metabolite 3-O-methyldopa - thus blocking the metabolism of the drug. Curently, there are two COMT inhibitors on the market: entacapone, acting on the peripheral metabolism of levodopa, administered together with levodopa (Olanow and Stocchi 2004) and tolcapone, more potent than entacapone and also acting within the central nervous system. Monoamine oxidase-B inhibitors (MAOBIs), such as deprenyl, rasagaline also induce fewer motor complications than levodopa after more than two years (Caraceni & Musicco 2001).

(ii) Transdermal delivery

a. a patch containing a new dopamine agonist, rotigotine to be applied every 24 hours (Metman et al. 2001).

(iii) Infusion therapies

a. intravenous Levodopa (Shoulson et al. 1975) was historically the first reported CDS treatment causing a virtual disappearance motor fluctuations in 5 fasting patients;
b. subcutaneous application of apomorphine (Manson et al. 2002, Katzenschlager et al. 2005) and lisuride (Stocchi et al. 2002): these two dopamine agonists are delivered subcutaneously with a pump mostly for waking time, with a good motor improvement

without motor fluctuations for many years. They both have a very short half-life and their beneficial effect is ascribed to continuous administration;

c. duodenal infusion of levodopa (Nyholm et al. 2005): this involves continuous delivery of a gel formulation of levodopa/carbidopa into the duodenum via a percutaneous tube and a portable pump.

In most cases, parenteral therapy is administered during waking hours only. Indications for continuous day-and-night dopaminergic receptor stimulation include severe sleep disturbances and off-related profound autonomic dysreguation. In such cases the nighttime dose should be halved in order to avoid eventual neuroplastic changes with behavioral sensitization and tolerance.

(v) Deep brain stimulation (DBS) passes a high-frequency electrical current into the target area mimicking the effect of lesioning the stimulated area. DBS of the subthalamic nucleus is an established surgical alternative for the treatment of motor fluctuations and dyskinesia in patients with advanced Parkinson's disease (Volkmann 2007). However, this treatment requires invasive surgery and is appropriate for a limited segment of the patient population.

While there is little doubt that the concept of steady-state plasma levodopa levels and continuous dopaminergic stimulation are emerging as an important concept in the treatment of Parkinson's disease, the choice of the therapy will depend on the disease characteristics, the age of the patient, cognitive (dys)function, other comorbidities, insight of the patient into the nature of the disease and the logic of its treatment and the willingness, ability of the carer to participate in the treatment process. Patients on continuous duodenal levodopa/carbidopa therapy receive it mostly as monotherapy, whereas patients on subcutaneous infusions of apomorphine or patients after DBS often require additional therapy, most often low doses of levodopa in order to improve non-motor symptoms.

Realities

- CDS treatments prove that central pharmacodynamic changes associated with long-term intermittent dopaminergic stimulation appear to be reversible, at least to some extent;
- CDS treatments convincingly stabilise the motor fluctuations in patients with advanced PD (Nutt et al. 2000), even the unpredictable on-offs;
- CDS treatments demonstrate antidyskinetic effects which may be related to desensitization;
- abruptly switching back to intermittent therapy does not immediately revert the patients to their baseline severity of motor fluctuations; this occurs after a few days.

Myths

- ‘enteral infusions can mimic the function of the normal dopaminergic brain’: this is not correct in the clinical setting, as milder fluctuations do occur with the CDS treatment;
- ‘around-the-clock constant-rate administration is without risk’: it does theoretically carries the risk of causing refractory off periods associated with severe immobility and hyperpyrexia;
- ‘CDS does not diminish motor response’: however, the antidyskinetic effects may be related to desensitization which could theoretically lead to a reduction in the amplitude of motor response (Nutt 2007);
- -‘CDS does not induce tolerance’: but clinicians are well aware of shortening of the motor response to levodopa over time which may be due to tolerance;
- ‘CDS does postpone or minimises future genesis of fluctuations in the clinical setting’: this has not yet been proven unequivocally, although some studies hint at it (Stocchi et al. 2002)

REFERENCES

1. *Bibbiani F, Costantini LC, Patel R, Chase TN. Continuous dopaminergic stimulation reduces risk of motor complications in Parkinsonian primates. Exp Neurol 2005;192: 73-78.*
2. *Calon F, Grondin R, Morissette M, et al. Molecular basis of levodopa-induced dyskinesias, Ann Neurol 2000; 47: S70-78.*
3. *Caraceni T, Musicco M. Levodopa or dopamine agonist, or deprenyl as initial treatment for Parkinson's disease. A randomized multicenter study. Parkinsonism Relat Disord 2001; 7:107-114.*
4. *Inoue M, Katsumi Y, Hayashi T, et al. Sensory stimulation accelerates dopamine release in the basal ganglia, Brain Res 2004;1026: pp. 179-184.*
5. *Katzenschlager R, Hughes A, Evans A, 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.*
6. *Manson A J, Turner K, Lees A J. Apomorphine monotherapy in the treatment of refractory motor complications of Parkinson's disease: long-term follow-up study of 64 patients. Mov Disord 2002; 17: 1235-1241.*
7. *Metman L V, Gillespie M, Farmer C, et al. Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease. Clin Neuropharmacol 2001; 24:163-169.*
8. *Mouradian M M, Juncos JL, Fabbrini G, et al. Motor fluctuations in Parkinson's disease: pathogenetic and therapeutic studies. Ann Neurol 1987; 22: 475-479.*
9. *Nutt J G, Obeso J A, Stocchi F. Continuous dopamine-receptor stimulation in advanced Parkinson's disease. Trends Neurosci 2000; 23: S109-115.*
10. *Nutt JG. Continuous dopaminergic stimulation: Is it the answer to the motor complications of Levodopa? Mov Disord. 2007;22(1):1-9.*
11. *Nyholm D, Nilsson Remahl A I, Dizdar N, et al. Duodenal levodopa infusion monotherapy vs oral polypharmacy in advanced Parkinson disease. Neurology 2005; 64:216-223.*

12. *Olanow CW, Stocchi F. COMT inhibitors in Parkinson's disease: can they prevent and/or reverse levodopa-induced motor complications? Neurology 2004; 62(Suppl. 1):S72-81.*
13. *Sarre S, De Klippel N, Herregodts P, et al. Biotransformation of locally applied levodopa in the corpus striatum of the hemi-parkinsonian rat studied with microdialysis, Naunyn Schmiedebergs Arch Pharmacol 1994; 350: 15-21.*
14. *Schultz W. Behaviour-related activity of primate dopamine neurons. Rev Neurol (Paris) 1994; 150: 634-639.*
15. *Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology. 1975;25:1144-1148.*
16. *Skirboll S, Wang J, Mefford et al. In vivo changes of catecholamines in hemiparkinsonian monkeys measured by microdialysis. Exp Neurol 1990; 110: 187-193.*
17. *Sossi V, de la Fuente-Fernandez R, Schulzer M, et al. Age-related differences in levodopa dynamics in Parkinson's disease: implications for motor complications. Brain 2006;129: 1050-1058.*
18. *Stocchi F, Ruggieri S, Vacca L, et al. Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 2002; 125: 2058-2066.*
19. *The Parkinson Study Group. Pramipexole vs levodopa as initial treatment for Parkinson disease. A 4-year randomized controlled trial. Arch Neurol 2004;61: 1044-1053.*
20. *Verhagen Metman L M M. Levodopa therapy of Parkinson's disease and associated long-term motor response complications, LeWitt PA, Oertel, W.H (eds.), Parkinson's Disease, The Treatment Options 1999; London: Martin Dunitz, 117-139*
21. *Volkmann J. Update on surgery for Parkinson's disease. Curr Opin Neurol. 2007; 20:465-469.*

Correspondence:
Zvezdan Pirtošek
Department of Neurology, University Medical Centre
Zaloška 2, SI-1000 Ljubljana, Slovenia
E-mail: zvezdan.pirtosek@kclj.si