

TREATMENT OF ADVANCED PARKINSON'S DISEASE AND ASSOCIATED PSYCHIATRIC DISTURBANCES

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Abstract

Parkinson's disease is a neurodegenerative disease, with increasing incidence, but with important therapeutic development in the last 50 years. Besides the 7 classes of oral medication used in all the stages of the disease, three types of invasive treatment are reserved for the advanced stages of Parkinson's disease, associated to the oral medication, or less frequent as monotherapy: apomorphine, levodopa-carbidopa intestinal gel (Duodopa[®]) and deep brain stimulation (DBS). A careful analysis of the patient, age, co-morbidities, psychosocial and economic factors is necessary to decide which treatment is suitable in each case. To increase patients' and caregivers' quality of life associated non-motor symptoms should also be treated, especially psychiatric disturbances (anxiety, depression, psychosis, and dementia) as well as comorbidities.

Rezumat

Boala Parkinson este o afecțiune neurodegenerativă, cu incidență în creștere, în tratamentul căreia s-au făcut progrese mari în ultimii 50 de ani. Pe lângă cele 7 clase de medicamente orale utilizate în toate fazele bolii, trei tipuri de tratamente invazive sunt rezervate bolii Parkinson avansate, în asociere cu cele orale sau ca unică terapie: apomorfina, gelul intestinal levodopa-carbidopa (Duodopa[®]) și stimularea cerebrală profundă. Alegerea unuia din cele trei tratamente presupune o riguroasă analiză a stării pacientului, a vârstei, comorbidităților, aspectelor psihosociale și economice. Pentru creșterea calității vieții pacientului cât și a persoanelor care se ocupă de îngrijirea acestuia se impune și tratarea concomitentă a simptomatologiei non-motorii, și în special a tulburărilor psihiatrice asociate (anxietate, depresie, psihoză, demență), cât și a comorbidităților.

Keywords: advanced Parkinson's disease, apomorphine, Duodopa[®], deep brain stimulation (DBS)

Introduction

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder, with an increasing incidence, due to a longer life expectancy. It's treatment developed in the last 50 years, starting from anticholinergics (trihexyphenidyl, biperiden, metixen), followed by L-Dopa associated with dopadecarboxilase (DDC) inhibitors (carbidopa and benserazide), catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone, and the newest opicapone), monoamineoxidase-B (MAO-B) inhibitors (selegiline, rasagiline, and the newest safinamide), dopamine agonists (ergot or non-ergot: lisuride, bromocriptine, alpha-dihydroergocryptine, pergolide, cabergoline, pramipexole, ropinirole, piribedil, apomorphine) and N-methyl-D-aspartate (NMDA) antagonists (amantadine, budipine). All these molecules were developed to improve especially motor symptoms such as bradykinesia, rigidity and tremor and in a lesser extent postural instability. Some of them can be used as monotherapy at the beginning of the disease, but all these groups of drugs can be used in association, according to the progression of the disease, based on their complementary effects, in very

complex ways (type of drug, dose, number of intakes, type of release), personalized for every patient, depending on the stage of the disease, clinical signs and symptoms, drug induced complications and co-morbidities [4].

Treatment options for PD advanced stages

Despite the optimized drug treatment, patients may show fluctuations regarding the effect, especially in advanced stages of PD, the most important cause being the discontinuous stimulation of the dopaminergic neurons [7].

Motor fluctuations: “on-off”, wearing “off”, delayed “on”, no-“on”, unpredictable “off”, dyskinesia in different associations may develop. Adverse effects of each drug or their association may reduce the benefits of treatment. The number of dopaminergic neurons diminishes, as well as their striatal and cortical connexions. Gastrointestinal disturbances (such as slow stomach emptying, slow intestinal movements) have negative effects on oral drug absorption.

For this group of patients in advanced stages of PD (Hoehn and Yahr stages ≥ 3 , 4 and 5 in “on” state), with very slow movements and needing permanent

help, with severe motor deficits and risk to fall, there are 3 more treatment options, having as a goal the continuous stimulation of the dopaminergic neurons. All of them are more or less invasive treatments. In this stage the management of motor fluctuations and dyskinesia and non-motor symptoms are also of great importance [8].

A good response to levodopa is essential before considering these 3 other treatment options. It is also important not to prolonged the time before starting one of these 3 treatments for advanced PD. Also, it is critical to choose the right treatment between apomorphine, Duodopa® (L-Dopa + carbidopa intestinal gel), using portable infusion pumps or deep brain stimulation (DBS). DBS is a neurosurgical procedure involving the implantation of a medical device called a neuro-stimulator. It is stereo-toxically implanted to specific parts of the brain and sends electrical impulses to targeted areas blocking the abnormal nerve signals that cause PD symptoms.

Apomorphine (APO) is the least invasive. It is the strongest dopaminergic agonist for D1 and D2 receptors but has also affinity for alpha adrenergic and serotonin (5-HT) receptors. It can be injected intermittent subcutaneously (in emergency due to the rapid absorption) or by continuous infusions using a small pump. It helps in treating “off” periods, but not dyskinesias. It has also effect on non-motor symptoms but cannot be used as monotherapy. It has a short half-life (maximum 60 minutes) and a lot of adverse events (cutanate nodules, dopaminergic adverse events), much more than the other 2 treatments [2]. Duodopa® (L-Dopa + carbidopa intestinal gel 4:1) has the same effects as the oral drug containing the same substances. A temporary catheter is placed through

the nose into the small intestine. If the patient responds well to this treatment, a permanent catheter is placed percutaneously, endoscopically, into the upper jejunum, using a gastro-stoma (PEG). This way the concentrated suspension is avoiding the stomach and is quickly absorbed into the blood, continuously stimulating the dopaminergic neurons, improving motor and non-motor symptoms (much better than apomorphine), having benefits for both “off” periods and motor complications. It can be used as monotherapy using 100 mL cassettes and portable infusion pumps. Adverse events are those of levodopa and some local ones associated with the tubing system or with gastrointestinal surgical procedures and demyelinating polyneuropathy [6]. There are clinical trials with continuous subcutaneous levodopa infusion which could replace the intrainstestinal delivery of levodopa.

Deep brain stimulation (DBS) is the most invasive treatment for advanced PD, using a stereotaxic procedure with implanted electrodes connected to a stimulator placed under the skin on the chest. The oral treatment is highly reduced if this procedure is implied. It is the most efficient on tremor, dyskinesia and hallucinations among these 3 treatments. It is suitable for younger patients living alone, but psychiatric adverse events are often described, as well as some local adverse events regarding the implantation of electrodes [5].

Considering the above mentioned therapeutic strategies, the question of choosing the best treatment arises.

The indications starting from the drug induced motor fluctuations are almost the same. The contraindications are different and refer especially to DBS (age, dementia, depression, psychosis) (Table I).

Table I

Treatments for advanced Parkinson’s Disease – indications. Modified after Antonini A, Odin P. Parkinson related Disorders 2009; 15; Suppl 4:97-100 [1]

	APO	DUODOPA®	DBS
Motor fluctuations	++	++	++
Dyskinesia	+	++	+++
Nocturnal rigidity	++	++	++
Tremor	-	-	++
Painful dystonia	-	-	++
Hallucinations	-	+	++
Age > 70 years	+	++	+/-
Severe dementia- Mini-mental state examination (MMSE) < 10	-	-	-
Moderate dementia	+	+	-
Drug induced psychosis	+/-	+	+/-
Depression, anxiety	++	++	-
Impulse control disorder	-	++	+
Risk of surgical complication	-	+	++
Technical complexity	-	+	++
Independence	+	+	++
Monotherapy	-	++	+
Co-morbidities	+	+	-
Multidisciplinary team	-	++	++
Indecision	++	+	-

MMSE = mini-mental state examination; APO = apomorphine; Duodopa® = levodopa-carbidopa intestinal gel; DBS = deep brain stimulation

Some patients are suitable for 2 or even all 3 treatments, so the neurologist, patient and caregiver have to discuss and decide which of these treatments is the best choice in order to have the best patient's and caregiver's quality of life.

To be sure that the described treatments will be helpful, there are also non-motor symptoms to be considered, among which the most important are the psychiatric disturbances as anxiety, depression, apathy, psychosis, impulsive-compulsive disorders and dementia.

Table II

Treatments for psychiatric associated disturbances

Anxiety	Depression	Psychosis	Dementia
benzodiazepines	pramipexole	clozapine	rivastigmine
SSRIs	TCAs	quetiapine	donepezil
SNRIs	SSRIs	risperidone	galantamine
TCAs	SNRIs	rivastigmine	memantine
	ECT	donepezil	
	psychotherapy		
	CBT		

SSRIs = selective serotonin reuptake inhibitors; SNRIs = serotonin-noradrenalin reuptake inhibitors; TCAs = tricyclic antidepressants; ECT = electroconvulsant therapy; CBT = cognitive behavioural therapy.

The most common disturbance is depression and can be treated using various treatments: psychotherapy, cognitive behavioural therapy (CBT), talk therapy; dopaminergic agonists (pramipexole, pergolide); selective serotonin reuptake inhibitors (SSRIs) – citalopram, sertraline, paroxetine; serotonin-noradrenalin reuptake inhibitors (SNRIs) – venlafaxine, duloxetine; tricyclic antidepressants (TCAs) nortriptyline, desimipramine; electroconvulsant therapy (ECT). Clinical trials were performed with pimavanserin a 5HT_{2a} agonist designed for psychosis and the drug was approved by the Food and Drug Administration (FDA) and istradefylline, the first non-dopaminergic therapy for Parkinson's disease. Istradefylline is an adenosine A2A receptor antagonist, effective on motor symptoms, fluctuating Parkinson's disease, depression, anxiety and memory impairment [3]. The advanced stage of PD known also as “the complex phase” associates some other non-motor symptoms: sleep disorders, arterial hypotension, gastrointestinal disturbances, urinary and sexual dysfunctions, pain, sweating, drooling. The neurologists should consider and discuss all these problems, should use specific scales to quantify them, and try to find solutions for all of them in order to improve the quality of life of the patients and their caregivers.

Conclusions

The management of advanced stage PD is challenging. The main goal should be to maintain acceptable levels of functioning.

The therapeutic strategies should be directed to create a balance between the benefits and the side effects of available drugs, also including strong and supportive services.

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