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Advances in Drug Therapy: Alternative Treatments for the Control of Motor Fluctuations and Dyskinesias

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1. Introduction

The treatment of Parkinson's Disease (PD) remains largely symptomatic and it controls effectively motor symptoms of the disease for some years. This is a treatment that is considered basically substitute, which only acts on the nigrostriatal pathway but does not provide adequate plasma levels 24 hours a day in most cases. As a result, conventional medication, especially levodopa, produces pulsatile stimuli that with the progression of the disease is associated with the development of motor complications (Markham & Diamond, 1986).

In recent years new formulations and alternative therapies (dopamine receptor agonists extended release, rotigotine patch, continuous infusion of apomorphine and continuous duodenal infusion of Duodopa) have been introduced in order to avoid pulsatile stimulation and thus prevent the "peaks " and "valleys" and achieve continuous dopaminergic stimulation to avoid, reduce or control the motor fluctuations and dyskinesias. Thus concept of continuous dopaminergic stimulation is born, which is not intended to restore modulatory physiological role exerted by dopamine on striatal function but to explain the benefits of using drugs that provide a more uniform and consistent dopamine stimulation, which has proven to be most appropriate and in practice more beneficial than traditional treatments. This review focuses on the treatment for symptomatic control of Parkinson's disease and complications from chronic treatment, the usefulness of new dopamine agonists and the beneficial effect of Duodopa as a possible alternative in the treatment of advanced PD compared with subcutaneous apomorphine infusion or deep brain stimulation of the subthalamic nucleus, this latter effective to control of motor complications but applicable to a very selective population with no cognitive or behavioral complications.

It is clear that oral Levodopa combined with peripheral inhibitory amino-acid decarboxylase remains still the gold standard in the treatment of PD 40 years later after their use by Cotzias. However, chronic treatment with levodopa (LD) is related to the onset of motor complications in form of fluctuations in the response with wearing-off phenomenon and dyskinesia, which may occur after 3 to 5 years after the start of the LD (Markham & Diamond, 1986; Marsden, 1994). This variability in motor response is correlated with the

fluctuation in plasma concentration of LD (related to oral intermittent delivery and irregular gastric emptying) and consequently with the level of pulsatile stimulation of dopamine receptors in the striatum (De la Fuente-Fernández et al., 2001). As the disease progresses, the therapeutic window is narrowed in such a way that reduces the response time "on" increases the off time and is easily reached the threshold for dyskinesias. Motor complications and the also increasingly important non-motor complications are being accentuated with the worsening of the disease and therefore impacts the quality of life of patients (Dodel et al., 2001; Clarke et al., 2002; Witjas et al., 2002).

2. Medical treatment

2.1 Dopamine agonist

Different strategies have been developed to achieve greater continuous dopaminergic stimulation with the sole purpose of delay, reduce or avoid fluctuations (Holloway et al., 2004; Rascol et al., 2006). These options include the administration of dopamine agonists (DA) which have proven effective in both the early stage of the disease and in the moderately advanced stage, improving motor symptoms and delaying the onset of motor complications resulting from the use of LD (Hauser et al., 2007). However, one of the biggest problems of AD has been the need for a slow titration to ensure good tolerance and therefore a delay in obtaining clinical benefits. The new formulations of extended-release agonists provide the advantage of producing a continuous release ensuring sustained absorption over 24 hours and reducing plasma fluctuations (Tompson & Vearer, 2007). Certainly in the treatment of PD, non-ergot dopamine agonists are considered first-line therapy in a substantial proportion of patients.

2.1.1 Ropinirole prolonged-release (RPR)

Perhaps one of the most interesting contributions was the fact that in a recent study, prolonged release ropinirole has shown good tolerance with higher starting dose than immediate release ropinirole and this results in a faster titration (Stocchi et al., 2008) and better clinical response significantly in a period of 4 weeks compared with placebo (Herh et al., 2010). It has been proven non-inferiority of therapeutic response with respect to the formulation of immediate response in monotherapy and in early stages of the disease (Stocchi et al., 2008). Its effectiveness has also been tested in advanced stage patients which not adequately controlled with levodopa, in a randomized, double-blind, placebo for 24 weeks, with a significant reduction in off time of 2.1 hours against 0.3 hours compared to placebo group, and improved quality of life PDQ (Pahwa et al., 2007). Due to the effect observed for 24 hours with this new formulation, several aspects of sleep and nocturnal symptoms improve. As a side effect, RPR causes sleepiness and fatigue which remain practically the same percentage as the immediate release formulation. Finally it is expected a better adherence to the administration once a day.

2.1.2 Delayed pramipexole

Another interesting alternative in the non-ergot-AD group is the new long acting formulation of pramipexole, administered once daily to maintain stable levels 24 hours. It has proven effective in improving parkinsonian symptoms in the early stages of the disease and in

advanced patients with motor fluctuations resulting in a decrease in off time compared to placebo. No differences in the tolerance respect the immediate release form and the side effects are also comparable (Poewe, 2008; Schapira, 2007). Perhaps the most important indication when compared to immediate-release pramipexole is the fact that it improves treatment adherence in PD.

2.1.3 Rotigotina

Rotigotina is the only non-ergot D3/D2/D1 AD with a formulation which allows for transdermal administration which is very important when it is necessary to reduce the oral medication. Its bioavailability is 37%, its active ingredient is released into the skin during 24 hours (Chen et al., 2009), reaching concentrations that are stable for 24 hours (Chen et al., 2009; Reichmann, 2009) and it has a low risk of accumulation due to its half-life of about 5-7 hours. It is administered by a transdermal patch of silicon and due to its lipophilic, follicular and eccrine properties rotigotine penetrates the skin by transcellular and intercellular pathways, providing a constant supply. It is rapidly metabolized and eliminated by renal and hepatic via and it avoids first-pass effect.

Studies in early stages of the disease support the efficacy compared with other agonists. In addition there is a better tolerance in relation to classical complications such as drowsiness, orthostatic hypotension and hallucinations, but on the other hand must be taken into account cutaneous reactions (The Parkinson Study Group, 2003; Giladi et al., 2007). It has also shown efficacy in advanced stages compared with oral agonists (Poewe et al., 2007), facilitating its administration when complications occur, such as dysphagia, alteration of intestinal transit and when the patient requires absolute diets such as in preoperative and postoperative situations (Korczyn et al., 2007.) Another interesting aspect is its possible effect on non-motor disorders of PD, mainly on the improvement of quality of sleep by improving other aspects such as akinesia, dystonia, nocturia and nocturnal cramps, without worsening daytime sleepiness (Giladi et al., 2006). RECOVER study results support the improvement of sleep disorders by PDSS scale and UPDRS-III scores on awakening (Trenkwalder et al., 2009).

2.1.4 Apomorphine

Apomorphine was the first dopamine receptor agonist used to treat Parkinson's disease over 60 years ago (Schwab et al., 1951; Cotzias et al., 1970). It is an a short-term agonist dopamine that direct acts on D1 and D2 receptors (Kempster et al., 1990; Colosimo et al., 1996), with clinical antiparkinsonian action very powerful, equivalent to the LD, both qualitatively and quantitatively. Apomorphine has a rapid absorption (C max 20 minutes) and a half-life of 43 minutes, which is consistent with its rapid onset of action with evident effects after 15-20 minutes of subcutaneous administration.

The efficacy of intermittent subcutaneous apomorphine has been confirmed in several studies (Poewe & Wenning, 2000; Pfeiffer et al., 2007). Moreover, the effectiveness of continuous subcutaneous apomorphine infusion apomorphine (CSAI) has been evaluated both in monotherapy as in addition to levodopa treatment in advanced PD. Several clinical studies support the CSAI to control motor fluctuations poorly controlled by conventional oral route. Apomorphine generally leads to an improvement on the time off between 50-80% and improves dyskinesias associated with LD (Katzenschlager et al., 2005). While the improvement in off time is constant in all studies, the improvement of

dyskinesias is less significant and is related to the reduction of the dose of LD. Moreover apomorphine in monotherapy can be achieved only at very high doses, usually above 100 mg / day, which are poorly tolerated by patients. Therefore most require a combination with oral LD, which in fact does not eliminate the effect of pulsatility and prevent the benefit on dyskinesia (Antonini & Tolosa, 2009). From the practical point of view we recommend pre-medicating the patient with domperidone at least three days before the start to prevent peripheral dopaminergic effects and alleviate or eliminate the effect of nausea and vomiting. Oral AD medication should be discontinued and start the infusion of apomorphine with 1 mg / hour maintaining the same dose of L-Dopa. The dose of apomorphine should be gradually increased depending on tolerance at the same time it should be gradually reduced the dose of L-dopa to reduce dyskinesias and if possible remove it completely.

However, the CSAI is not free of side effects, the most constant are the presentation of subcutaneous nodules (70-80%), sedation and somnolence (23%), nausea and vomiting (10%), renal failure (6%), positive Coombs test (6%) and orthostatic hypotension (5%). The adequate local hygiene and daily change of subcutaneous injection site are important measures to prevent panniculitis. (Antonini et al., 2009)

There is no clear definition of the best candidates. They are usually advanced PD patients with good motor response to L-dopa but inadequately controlled on oral medication and who have motor fluctuations. Patients with cognitive impairment, elderly, orthostatic hypotension, severe systemic disease and a history of dopaminergic psychosis must be excluded.

In a study of continuous subcutaneous apomorphine infusion realized in Spain from 2003 to March 2007 in 35 tertiary care hospital centers with a recruitment of 166 patients of whom 82 patients were selected with on-off fluctuations (96%), dyskinesias (48%), whose main objective was to improve the fluctuations, while the dyskinesias associated with L-dopa was not the main purpose unless very severe dyskinesias, with apomorphine dose continuous infusion between 35 mg and 160 mg/day for an average 14 hours per day the following results were found statistically significant: improvement in total UPDRS and motor UPDRS, reduction in the number of off hour per day and number of off episodes per day, reduction in dyskinesias and improvement in balance of gait, reduction in total dose of oral antiparkinsonian medication. Only 3 patients received CSAI in monotherapy, while only 20 needed oral L-dopa mainly in a morning standard dose or in a controlled release Ldopa at night. Most patients had side effects; the most common were subcutaneous nodules. Neuropsychiatric side effects were frequent and the most common have been hallucinations, hypersexuality, confusional state and other complications such as sedation, drowsiness, nausea, orthostatic hypotension and hemolytic anemia. About duration of the 82 patients studied, 27 had been received CSAI for over two years and 9 patients for at least 4 years (García Ruiz et al., 2008).

In conclusion CSAI is a non aggressive, easy to perform and relatively easy to control technique. Certainly the patient and family should have some skill in handling the device and must maintain scrupulous hygiene. This confirms once again that CSAI is effective for control of advanced PD with severe fluctuations that are not well controlled with conventional oral medication.

However, the real impact of CSAI in advanced PD is still a subject for debate.

2.2 Entacapone

Another option is the use of inhibition of catechol-O-methyltransferase (COMT), entacapone. It has been noted that its administration increases the levodopa half-life of over 85% and decreases its metabolite 3-O-methyldopa plasma concentrations (Nutt et al., 1994). However, we must consider that it may have a heterogeneous effect in patients. Thus patients with low COMT activity would obtain a low optimal effect, while patients with high activity would obtain better clinical effect but also increase risk of adverse effects. This is due to the existence of polymorphisms of the COMT, which enzyme activity is variable in the population and is related to the substitution of valine for methionine at codon 158 (Syvanen et al., 1997). In Several randomized controlled trial, in which we evaluated the adjuvant effect of entacapone versus placebo in patients with PD and motor complications, there is a significant reduction in off time, improved on time, decrease the dose of levodopa. Its main side effect is the presentation of nausea, vomiting and diarrhea, as well as dyskinesias that can be easily controlled with levodopa reduction (Pahwa et al., 2006). Their use has led to the hypothesis that if a continuous release of LD is gotten may reduce the risk of motor complications. This could be possible with the combination of LD with entacapone, an inhibitor of catechol-0-methyltransferase. This hypothesis recently led STRIDE-PD (Stalevo Reduction in Dyskinesia Evaluation), a multicenter, double-blind, randomized, flexible dose of levodopa (200-1000 mg), with monitoring between 134 and 208 weeks in 747 patients that require initiation of LD, in four doses per day, establishing two groups (LD and LD + entacapone stratified by use of AD at the beginning), which results did not support the early initiation of LD + entacapone reduces the risk of complications and delays the presentation of dyskinesias. There are an increase the risk and higher frequency of dyskinesias in the subgroup of patients taking AD, whereas in the subgroup not taking agonists there are no difference in the time of onset of this complication. The wearing-off occurs more frequently in the LD group than in the LD + entacapone group, but the start time of wearing-off was similar in both groups. This result was not affected by the use of agonists (Stocchi et al., 2010).

2.3 Duodopa

Duodopa is a recent use drug. It is a suspension of micronized levodopa in a methylcellulose thickener gel, which was initially used as compassionate use, but since 2004 its indication was approved in several European countries in advanced PD. At this stage of the disease, levodopa infusion via the gut is an important alternative because it reduces the fluctuations of plasma LD levels and therefore improves the motor response unresponsive to conventional oral therapy (Nyholm et al., 2008), however it should be subject to selection criteria (table 1).

<ul style="list-style-type: none">- PD with disabling motor fluctuations (ON-OFF phenomena)- Lack of efficacy of conventional treatments- Response to levodopa, preferably with some quality ON periods- Preferably with no cognitive impairment or mild cognitive impairment- Without psychiatric or behavioral disorders- No age limit (good condition)- Good family or social support
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Table 1. Choosing the right candidate

2.3.1 Infusion intrayeyunal of duodopa: control of motor and non motor symptoms

Intrayeyunal infusion of gel levodopa/carbidopa (Duodopa) may represent the more physiological treatment of motor complications in advanced PD using the concept of continuous dopaminergic stimulation observed LD plasma stability compared with oral therapy. Numerous studies have shown a reduction in off-time, an increase in on-time, reduction the severity of dyskinesias and their duration, including patients with deep brain stimulation therapy whose results have been insufficient or ineffective (Antonini et al., 2008). Compared to other options such as subcutaneous apomorphine infusion and DBS surgery, monotherapy with duodopa is usually achieved, avoiding therefore other pulsatile administration of additional medications (Antonini, 2007). DBS will not be discussed in this chapter.

However in advanced PD, motor symptoms are not the only major disruption but also the existence of non-motor symptoms (NMS) are often refractory to conventional treatment and contributes to a deterioration in the quality of life, stress and hospitalizations (Chaudhuri et al., 2006; Martínez-Martín et al., 2007) so in recent years have gained considerable recognition for the impact of these symptoms on quality of life (Chaudhuri et al., 2008). Non-motor signs of PD can be quantified using the non-motor symptoms scale (NMSS) that has been validated (Global Parkinson's Disease Survey Steering Committee, 2002). His assessment suggests that quality of life is strongly correlated with NMSS but only modestly with the score of the UPDRS III and IV. This observation has been endorsed by other studies. More recently, the highly significant benefit infusion Duodopa has been demonstrated in prospective studies by sleep scale, PDQ-8 and total score of the NMSS (cardiovascular, sleep / fatigue, mood / cognition, perception / hallucination , attention / memory, gastrointestinal, urinary, sexual, and miscellaneous (Honig et al., 2009).

These findings together with the recent publication of PDLIFE study, which shows a worsening of motor symptoms and NMS in patients undertreated, demonstrate the importance of global symptom control over the control of other focal symptoms (Grosset et al., 2007).

The observation of improvement in important domains of NMSS underscores the hypothesis that important aspects of the NMS may in part be related to the pathophysiology of dopamine. This finding is consistent with studies suggesting that depression, aspects of sleep dysfunction such as insomnia, restless leg syndrome, nocturia, pain, sexual dysfunction, apathy, and anhedonia are partly related to dysfunction of the dopaminergic system (Remy et al., 2005; Devos, 2009).

2.3.2 Complications

The infusion system of Duodopa includes infusion pump systems, internal and external connection to the jejunum and percutaneous gastrostomy. Any complications may present in any of these levels, the most common are unintentional disconnection of the tube, obstruction of the tube kinking or migration intestinal. Other complications related to gastrostomy as infection, local inflammation or peritonitis are rare. Complications can also occur due to the Duodopa itself such as psychosis, biphasic dyskinesias, behavioral changes with impaired impulse control, orthostasis, and hallucinations, usually easily controlled (Honig et al., 2009).

Adverse effects in relation to Duodopa (drowsiness, visual hallucinations, psychotic episodes, dizziness, headache) are similar to those seen with conventional levodopa

(Nyholm et al., 2005). There have been case reports of polyneuropathy of the Guillain Barre type (Antonini et al., 2007) and development of vitamin B12 and B6 deficiency polyneuropathy (Onofrij et al., 2009).

2.3.3 Conclusion

Duodopa can be summarized that is effective and safe, with significant benefit for the control of motor and non motor symptoms. Most problems are not serious and generally easy to solve, with favorable risk/benefit ratio. Its indication in patients with advanced PD with severe motor fluctuations and dyskinesias may represent an alternative to surgery and continuous infusion of apomorphine. The candidate selection is not as restrictive as in the other two techniques, so that patients which are not optimal for surgery and apomorphine can be treated successfully with Duodopa (Devos, 2009; Sánchez-Castañeda et al., 2010).

But despite clinical benefits, total number of patients treated with infusions is still limited due to the complexity of the procedure.

The general conclusions are:

1. Infusions provide constant plasma levels preventing the peaks and valleys that are typical of the medication orally.
2. Infusions can reduce dyskinesias and extend the therapeutic window in advanced PD.
3. Apomorphine is effective in reducing off time but improvement of dyskinesias is limited by the need to continue with oral L-dopa in most patients. Its use remains limited in time and its discontinuation is mainly due to the development of skin reactions.
4. Experience with continuous infusion of duodenal L-dopa/carbidopa shows that the benefit is also related to the quality of life and better control of non-motor symptoms such as cardiovascular system, bladder, gastrointestinal function and sleep quality

3. Behavioral disorders and their relationship with dopaminergic medication

In recent years interest has focused on behavioral disorders in Parkinson's Disease due to their higher prevalence than in the general population and its relation to dopaminergic therapy, primarily to the use of dopamine agonists. It includes impulse control disorders (ICD) such as pathological gambling, buying and compulsive food intake, hypersexuality and repetitive stereotyped behaviors-punding devoid of purpose and dopamine dysregulation syndrome also known as syndrome of addictive behavior, in which there is a progressive, increased and excessive consumption of dopaminergic drugs, higher than needed to control the motor symptoms of the disease despite the occurrence of severe dyskinesias. It develops a tolerance to the euphoric effect of dopaminergic therapy and often produces a state of abstinence because of the reduction or withdrawal of medication in addition to motor worsening, complicating the management of this type of addictive disorder.

The impulse control disorder is characterized by an inability to resist an impulse or temptation to perform an act that can be harmful to other or to themselves. It is very important to identify because it can cause significant distress to patients and caregivers, serious financial and socio-familiar consequences. Its key feature is the participation in a repetitive and compulsive behavior despite adverse consequences, an impulse of appetite or desire before engaging in the problematic behavior and a hedonic quality during the

execution of the act. It shares a conceptual resemblance to the drug addiction in which patients perform compulsive activity despite adverse consequences (Ceravolo et al., 2010).

Addictive behavior syndrome is a neuropsychiatric disorder of behavior associated with excessive use of dopaminergic drugs, more frequently with levodopa and apomorphine. The clinical features met the accepted criteria for addiction: compulsive use of drugs, hypomania, impulsivity, withdrawal symptoms such as anxiety and dysphoria. The psychiatric features include manic, elation, irritability, psychomotor agitation, paranoia towards hospital staff and family. Compulsive acts with stereotyped behaviors frequently occurs in this syndrome. These acts are characterized by an intense fascination for handling technical equipment repetitively and continuously or review and classification of common objects (Ceravolo et al., 2010).

The prevalence of these disorders varies according to the series. They are often underdiagnosed because not all patients are aware of the problem and they do not relate them to the PD. At other times patients are reluctant to admit the existence of these disorders. Recently in a large cross-sectional study of 3090 patients with idiopathic PD has been described the existence of any impulse control disorder in 13.6%, of which pathological gambling 5.0%, compulsive behavior of sex 3.5%, compulsive buying 5.7%, eating disorder 4.3%. Several disorders are often associated in the same individual 3.9%. This disorder occurs more frequently in patients taking AD (17.7%) compared to those who do not take (6.9%), finding no significant difference between Pramipexole 17.7% vs Ropinirole 15.5% (Weintraub et al., 2010).

In addition to individual factors, predisposing factors have been identified such as the duration of the disease, high doses of medication, especially AD unrelated to any specific (class effect) (Ceravolo et al., 2010) but may also occur at low doses, at lower age, at disease onset (Voon et al., 2006), the existence of affective disorders (Pontone et al., 2006) and a ICD before PD (Weintraub et al., 2006) and the presence of motor complications. However, no differences were found in Hoehn and Yahr stage between patients with and without ICD.

Treatment usually involves the reduction/suspension of AD, adjusting the dose of levodopa. If these measures are insufficient alternative pharmacological measures can be employed, though less user experience. Thus selective inhibitors of serotonin reuptake have proven effective in binge eating and stereotyped behaviors (Wolters et al., 2008). Atypical antipsychotics such as quetiapine are useful in pathological gambling and hypersexuality. In the latter case can be used antiandrogens such as cyproterone acetate (Klos et al., 2005).

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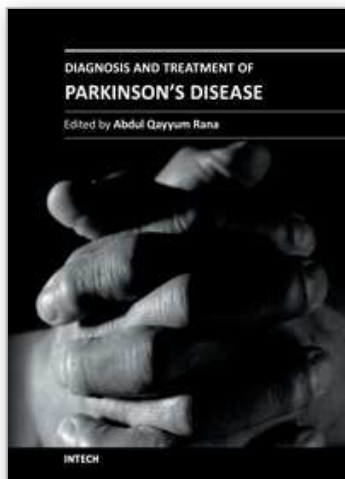
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Parkinson's disease is diagnosed by history and physical examination and there are no laboratory investigations available to aid the diagnosis of Parkinson's disease. Confirmation of diagnosis of Parkinson's disease thus remains a difficulty. This book brings forth an update of most recent developments made in terms of biomarkers and various imaging techniques with potential use for diagnosing Parkinson's disease. A detailed discussion about the differential diagnosis of Parkinson's disease also follows as Parkinson's disease may be difficult to differentiate from other mimicking conditions at times. As Parkinson's disease affects many systems of human body, a multimodality treatment of this condition is necessary to improve the quality of life of patients. This book provides detailed information on the currently available variety of treatments for Parkinson's disease including pharmacotherapy, physical therapy and surgical treatments of Parkinson's disease. Postoperative care of patients of Parkinson's disease has also been discussed in an organized manner in this text. Clinicians dealing with day to day problems caused by Parkinson's disease as well as other healthcare workers can use beneficial treatment outlines provided in this book.

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