LEVODOPA THERAPY FOR PARKINSON'S DISEASE

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Abstract

January 2023 marks the 100th anniversary of the birth of Arvid Carlsson, a Swedish scientist, one of the three winners of the Nobel Prize in Medicine in 2000 "for proving that dopamine is a brain neurotransmitter whose deficiency leads to the symptoms of Parkinson's disease". Levodopa therapy is one of the main achievements of neurology in the twentieth century and Parkinson's disease was the first disease in which a specific neurochemical deficiency was confirmed in defined regions of the brain, which forms the basis for rational, chemically supported therapy.

This paper briefly reviews the most important achievements in the discovery of dopamine and levodopa, as well as their functions in the development of Parkinson's disease. Dopamine synthesis, understanding of levodopa synthesis method, the possibility of measuring dopamine concentration in putamen and caudate and its loss in Parkinson' s disease, along with histochemical visualization of nigrostriatal pathway and animal lesion model, enabled understanding of the role of nigrostriatal dopamine system in the development of Parkinson's disease symptoms.

Part of the work is devoted to the metabolism of dopamine in healthy dopaminergic neurons and to its functioning in dopaminergic neurons of Parkinson's disease patients. It is known that in Parkinson's disease dopamine deficiency occurs due to selective degeneration of nigrostriatal dopaminergic neurons. Their suffering is triggered by a cascade of events that included the action of potential toxins, the influence of susceptibility genes on the body's response to them, oxidative stress caused by mitochondrial dysfunction, and dysfunction of the ubiquitous proteasomal system, which leads to the accumulation of incorrectly "packaged" proteins, the exhaustion of the endoplasmic reticulum system and the activation of mycroglia that follows inflammatory process. These changes can lead to programmed cell death of dopaminergic neurons with consequent dopamine deficiency and the development of Parkinson's disease. Special attention is paid to the consequences of neuron loss on the functioning of the remaining dopaminergic neurons and dopamine receptors, regarding the therapeutic motor complications that may arise on that occasion. The basic assumptions about the occurrence of therapeutic complications are still related to the pharmacokinetics of levodopa and the model of its delivery to the brain, which results in non-physiological, pulsatile stimulation of dopamine receptors. Today's possibilities in achieving more stable concentration of levodopa with existing strategies are presented with an answer to the question of whether continuous stimulation can be achieved under the conditions of standard regular patients' levodopa therapy. In the short final part, is a comment of the position of levodopa in the guidelines and recommendations for treatment. It is expected that L-dopa will remain the "gold standard" for the treatment of Parkinson's disease, at least until the development of more potent and safer dopamine agonists or the development of neuroprotective or neurorestorative therapies.

Keywords: dopamine, levodopa, Parkinson's disease

Introduction

Choosing a topic that would be related to new knowledge and current events in the field of degenerative brain diseases, one date took me back in time and I decided to

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write about dopamine and its precursor - levodopa. January 2023 would be the 100th anniversary of the birth of Arvid Carlsson, Swedish scientist, one of the three winners of the Nobel Prize in Medicine in 2000 "for proving that dopamine is a brain neurotransmitter, which deficiency leads to the symptoms of Parkinson's disease." In a commentary on his research, Andrew Lees noted that the classic physiological experiments that led to Carlsson's Nobel Prize "owed little to chance, and much more to self-confidence and determination to support his hunch and pave the way for what we would call a dopamine miracle"[1]. The centenary of Carlsson's birth was only an immediate cause to write about research on dopamine and dopamine transmission in the development and treatment of Parkinson's disease (PD), but L-dopa certainly deserves to be talked about. Levodopa therapy is one of the main achievements of twentieth century neurology, and PD was the first disease in which a specific neurochemical deficiency was confirmed in defined regions of the brain, which formed the basis for rational, chemically supported therapy. Carlsson, on the other hand, was one of the most significant participants of the "dopamine/Parkinson's disease/levodopa drama", whose significant results were created at the moment when the new knowledge was acquired. That enabled a crucial step forward, which turned knowledge into practice.

History

The exciting story of the discovery of dopamine begins with the isolation and chemical synthesis of L-dopa and dopamine (DA). DA was simultaneously chemically synthesized in London and Berlin in 1910[2, 3], while L-dopa was synthesized eleven years later[4]. Pharmacologically, dopamine was thought to be a weak sympathomimetic, similar to epinephrine[5] and represented, along with L-dopa, a possible precursor of epinephrine. Holz and Blaschko in 1939 independently assumed that the biosynthetic pathway of catecholamines (norepinephrine and epinephrine) goes via L-dopa and dopamine, and both represented metabolic intermediates in this biosynthetic pathway[6]. When tyrosine hydroxylase[7], which participates in the synthesis of L-dopa from tyrosine was discovered in 1964, the understanding of the dopamine synthesis pathway was completed.

The understanding of the role of DA in the brain and its role in motor skills and behavior came from the discovery of reserpine, an alkaloid extract from the root of the plant *Rauvolfia serpentine*. Indian researchers noticed that *Rauwolfia* extracts can cause parkinsonism, and that after its introduction for the treatment of hypertension, a high percentage of those treated, as well as those in whom reserpine was administered for the purpose of treating schizophrenia, developed parkinsonism[8]. Arvid Carlsson investigated the effect of reserpine on brain functions and its biochemistry. The key to his research was the development of a highly sensitive biochemical technique for the quantification of dopamine[9], which enabled its measurement and evidence of its high concentration in the striatum, i.e. its specific regional distribution. He noted that the lack of dopamine caused by reserpine in experimental animals was the basis for the emergence of a condition similar to parkinsonism, the symptoms of which could be alleviated by the use of levodopa[10]. These results initiated the idea that L-dopa could also be effective in the treatment of PD in humans by compensating for deficient DA[11-13].

Oleg Hornikievicz, after learning that dopamine is concentrated in the striatum and that L-dopa reversed reserpine-induced parkinsonism, measured dopamine from the brains of people with parkinsonism, healthy people, patients with Huntington's chorea and postencephalitic parkinsonism. He also showed that parkinsonism symptoms correlate with the degree of loss of striatal dopamine[14].

The development of a special biochemical technique also enabled the visualization of cells containing biogenic amines[15]. Cell bodies were localized in the *pars compacta substantia nigra* (SN) and their nerve endings reached the striatum.

An experiment on monkeys showed that the lesion of the SN is accompanied by the loss of DA in the neostriatum[16, 17]. This completes the whole picture, starting with the biochemical discoveries of DA concentration in the putamen and caudate, and its loss in the PD, conjointly with histochemical visualization of the nigrostriatal pathway and an animal lesion model, which displays the role of the nigrostriatal dopamine system in the development of PD symptoms.

Until the Cotzias showed that high doses of L-dopa could dramatically reverse most of the motor symptoms of PD, the medical community did not believe in its therapeutic value, especially due to the fact that even its low doses caused gastrointestinal side effects (mainly nausea and vomiting). In 1969 Cotzias and his colleagues reported achieving remarkable clinical efficacy with L-dopa in PD patients by administering high doses to produce sufficient DA in the brains of the patients[18].

Melvin Yahr recognized Cotzias success and immediately conducted a double-blind study to support the conclusions, and published the results in 1969 Yahr and his colleagues[19] followed 60 subjects: 56 with PD, three with postencephalitic parkinsonism, and one with atypical parkinsonism (progressive supranuclear paralysis). 54 subjects were observed long-term and evaluated (4-12 months). The degree of improvement was greater than 50% in 34, 20% to 49% in 16, and only in four subjects the degree of improvement was less than 20%.

These studies were followed by trials that led to L-dopa being approved by the US Food and Drug Administration (FDA) in 1970[20]. Since then, it has never lost its most important role in the treatment of PD.

Dopamine in healthy dopaminergic neurons

In healthy dopaminergic neurons, dopamine is synthesized from L-dopa as the first of the three catecholamine neurotransmitters (DA, noradrenaline/norepinephrine and adrenaline/epinephrine) under the action of dopa decarboxylase (DDC)[21], while L-dopa, on the other hand, is synthesized from tyrosine by tyrosine hydroxylase (TH)[7]. In melanin-producing melanocytes, tyrosinase also produces L-dopa indirectly as an intermediate product from tyrosine[22].

Metabolism of L-dopa on the periphery is catalyzed, except with the help of decarboxylase of aromatic amino acids (dopa decarboxylase) and through monoamine oxidase (MAO) and catechol O-methyltransferase (COMT). Administration of peripheral dopa decarboxylase inhibitors (carbidopa, benserazide), which do not cross the blood-brain barrier, could increase the level of L-dopa in the blood and its availability in the brain. Later, it was found that COMT[23] inhibitors also inhibit the peripheral metabolism of L-dopa and thus increase the availability of L-dopa. The COMT inhibitor entacapone does not cross the blood-brain barrier and increases the availability of L-dopa by inhibiting peripheral COMT.

Dopamine in the human brain is primarily oxidized via MAO B. Therefore, MAO B inhibitors are expected to protect DA against its degradation[24]. COMT is responsible for the metabolic inactivation of dopamine as well as L-dopa[25, 26]. Entacapone, a COMT inhibitor, does not cross the blood-brain barrier and cannot affect its metabolism centrally, but tolcapone, also a COMT inhibitor, passes through and affects the synthesis and metabolism of DA in the brain[27].

Dopamine in the dopaminergic neurons of a patient with PD

Today we know that in PD, dopamine deficiency is caused by selective degeneration of nigrostriatal dopaminergic neurons. Their suffering is triggered by a cascade of events that includes the action of potential toxins, the influence of susceptibility genes on the body's response to them, oxidative stress caused by mitochondrial dysfunction, dysfunction of the ubiquitin proteasomal system that leads to the accumulation of incorrectly "packaged" proteins, the exhaustion of the endoplasmic reticulum system and the activation of mycroglia that accompanies the inflammatory process. These changes may lead to programmed cell death of dopaminergic neurons with consequent dopamine deficiency and development of PD[28, 29].

The injured nigrostriatal dopaminergic neurons in the PD brain cannot convert exogenously administered levodopa into dopamine. However, exogenously ingested L-dopa can still be decarboxylated to DA, primarily within aromatic amino acid decarboxylase (AADC) containing cells that exist in the striatum, such as serotonergic neurons and glial cells[30]. There are controversial opinions regarding the functionality of DA produced in non-DA cells. While there are still preserved dopaminergic neurons, DA produced from exogenously administered levodopa can be taken up into residual DA neurons by DA transporters, and stored in DA synaptic vesicles by vesicular monoaminergic transporter 2 to be later prepared and used for neurotransmission. However, since in advanced PD, DA produced from exogenous L-dopa in non-DA cells will not be able to be transported into DA neurons and stored in synaptic vesicles, it can only act directly on postsynaptic DA receptors, like other dopamine agonists. It is believed that this situation creates the conditions for the development of motor complications of long-term treatment with levodopa.

Motor skills complications include fluctuations in motor response and dyskinesia (LID). They are divided according to the temporal connection with the dose of levodopa taken and according to the clinical motor and sensory phenomena with which they are presented in table 1.

Fluctuations of the motor clearance

There is a common pattern of progressive worsening of motor response in levodopa-treated patients. The first event that occurs is the loss of effectiveness at the end of the dose-wearing off effect, when with the duration of the disease it is noted that the previously adequate dose of levodopa does not last as before (at least 4 hours). It is assumed that the basis of this problem is the process of suffering of dopaminergic neurons and the loss of their ability to store dopamine, which has already been discussed.

Table 1. Motor fluctuations and dyskinesia as a complication of long-term treatment with levodopa

Complications	Symptoms	
Fluctuations	Wearing off Sudden off Sudden, random off	Super off Yo-Yo fenomen Delayed on
Dyskinesias	Peak of dose chorea, balism and dystonia Biphasic chorea and ballism End of dose dyskinesia Off dystonia Myoclonus	Simultaneous occurrence of dystonia and parkinsonism Sudden occasional frizz Weakening of response at the end of the day The response depends on the consumed meal Occasional absence of response (dose failure)
Sensory, behavioral and autonomic off-s	Pain, Akathisia, Depression, Anxiety, Dysphoria	Panic attacks, Profuse sweating Abdominal bloating Dyspnoea, Micturition urgency

Namely, at the beginning of levodopa administration in PD patients, there is a so-called long-duration response to levodopa, which probably depends on the ability of surviving neurons to store and convert levodopa into dopamine, which is then released as needed, due to which the motor response remains stable. Later, during the development of the "wearing-off" phenomenon, the short-duration response becomes dominant (the motor response follows the concentration of levodopa in the

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plasma because the remaining neurons do not have the ability to store and convert it into dopamine), which leads to a shortening of the effect of a single dose of the drug[31].

An interesting study by Fabrini et al. in 1987 showed that in fluctuating patients, those who do not fluctuate, patients with on-off phenomena and those who have never been treated, after turning off levodopa infusion, levodopa levels in the plasma as a function of time, behave the same in all subjects[32]. However, despite similar plasma drug levels, the patient's clinical condition changed and worsened more rapidly in those with motor complications, which supports the levodopa storage hypothesis presented earlier. These findings are important because of the conclusion that the problems of fluctuations could be solved and treated by stabilizing the plasma level of dopamine (maintaining the plasma level of dopamine will also keep the motor response stable)[33].

It is likely, however, that apart from the described central mechanisms (reduced storage capacity), levodopa itself with changes in its peripheral pharmacokinetic and pharmacodynamic characteristics, plays an important pathophysiological role in the occurrence of motor fluctuations. Murata and Kanazawa in 1993 showed that repeated administration of levodopa induces acceleration of absorption of levodopa from the bowels and across the blood-brain barrier, reduction of dopamine oxidation in the striatum and loss of the "supersensitive" response of dopamine receptors[34]. It has also been shown that long-term therapy with levodopa significantly increases the peak concentration of levodopa in plasma (Cmax), as well as the total exposure to the drug in time (area under the time-concentration curve - AUC), while the time to reach the maximum concentration and the elimination half-life is shortened[35]. This may explain the less "smooth" clinical response in patients with advanced disease in whom, due to problems with levodopa storage, everything depends on the externally administered drug, whose plasma concentration is additionally "capricious" due to altered levodopa pharmacokinetics (levodopa arrives as a "flood"- it appears intensely, and disappears quickly).

Unstable and variable concentration of levodopa results in non-physiological stimulation of dopamine receptors, which is not safe for them and causes a cascade of further pathological events. Namely, chronic non-physiological stimulation of tonically active striatal dopaminergic receptors activates a specific signaling cascade in striatal spiny dopaminergic neurons, on which glutamate receptors are simultaneously presented. This process results in the potentiation of NMDA - type glutamate receptors on gabaergic striatal efferent fibers. As a consequence of their increased sensitivity to excitation from cortical glutamatergic afferents, occurs on-off type fluctuations and dyskinesia[36].

A study with apomorphine, which does not depend on storage in presynaptic nerve endings and is a direct agonist of dopamine receptors, speaks of the equally important role of receptors. The anti-parkinsonian effect of apomorphine in patients with motor response fluctuations was lost earlier in fluctuating patients, than in persons with stable response[37].

By giving a continuous intravenous infusion of levodopa, which produced a stable plasma concentration, the subjects with fluctuations were gradually corrected, although the discontinuation of the therapy returned the condition to the original state. The authors hypothesized that the non-physiological stimulation of receptors may be the basis, not only of recovery, but also of the occurrence of motor fluctuations[38, 39], offering an idea for treatment as well as their prevention.

Dyskinesias

It is known that the greatest risk factors for the occurrence of dyskinesias are: the severity of the disease[40], the dosage of levodopa[41], the age at the onset of the disease[42] and the length of treatment with levodopa[43]. Dyskinesias caused by levodopa are probably related to the supersensitivity of dopamine receptors, so in this sense they will not occur in healthy people who have been given the drug, and in sick people they will occur primarily on the more severely affected side. This phenomenon places the state of dopamine receptors in the place of an important teammate in the development of dyskinesias. Evidence that dopamine receptors and the changes that occur on them during long-term treatment play a role, not only in the loss of the anti-parkinsonian effect but also in the occurrence of dyskinesias, was found in research that showed that a drop in levodopa plasma concentration leads to the disappearance of dyskinesias, rather than the loss of the antiparkinsonian effect. Namely, the time for the disappearance of dyskinesia is shorter than the time required for the loss of the antiparkinsonian effect of the drug. This statement is important, not only because it speaks of the role of altered sensitivity of dopamine receptors in the occurrence of dyskinesias, but also because it leads to the assumption that different types of dopamine receptors participate in the occurrence of dyskinesias and antiparkinsonian action[38, 39].

Mouradian et al. in 1988 published the results of a study in which they analyzed the antiparkinsonian effect in never treated, stable patients, people with wearing off and on-off phenomena. These patients also differed in the "window" between the dyskinetic and antiparkinsonian effect, which narrowed with the appearance of motor complications, and in this sense, with the progression of the disease, the difference between the dose that would condition the therapeutic response and the dose that would cause dyskinesias, decreased[44].

Postmortem analyzes in primates, ranked subjects into healthy, levodopa-treated Parkinson's patients without dyskinesias and those with dyskinesias[45]. The study showed that the occurrence of dyskinesias is linearly related to the sensitivity of the D1 receptor, which led to the conclusion

that dyskinesias is the result of increased activity of the D1 receptor at the level of the direct pathway. The complex mechanism of origin and incompletely clear etiopathogenetic mechanisms that condition the appearance of therapeutic complications are the reason that the treatment of motor complications in the advanced stage of PD is a real challenge.

Usually, in the case of dyskinesias, choreiform movements, dystonia and myoclonus are involved. The frequency of dyskinesias increases with the progression of the disease, so with an annual risk of 10%, after 10 years 100% of those treated will have this problem. It is believed that 30-50% of patients develop dyskinesias after five or more years from the onset of symptoms[46, 47]. While fluctuations in motor response (shortening of the effect of a single dose) appear after 8 years in 58% of treated patients (average 35 months), dyskinesias develop in an average of 7 months later, simultaneously with the frizzing[48]. They develop more often in younger patients and those treated with higher doses of levodopa. Many non-DA systems including noradrenaline, glutamate, GABA, histamine and cannabinoid may be involved in the generation of LID[49, 50].

Carta and colleagues[51] reported that the development of LID in rats with 6-OHDA-induced lesions of nigrostriatal DA pathways was critically dependent on the integrity and function of the serotonin system. Removal of afferent serotonergic fibers or suppression of serotonin neuron activity with selective agonists that regulate serotonin release resulted in almost complete blockade of LID. This suggests that dysregulated release of DA from serotonin terminals is a major driver of dyskinesias in PD rat models. In animals with complete DA lesions, the preserved serotonergic innervation was unable to sustain the therapeutic effect of L-dopa, suggesting that the release of DA as a "false neurotransmitter" from serotonin terminals is more harmful than beneficial. This concept is also supported by experiments indicating that serotonin neuron transplants exacerbate LID in a PD rat model[52].

Rommelfanger et al. reported that loss of noradrenaline in the *locus ceruleus*, produced more profound motor deficits, than that produced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in mice and that the mice exhibited spontaneous dyskinesias[53]. Loss of noradrenaline and DA may have a synergistic effect on the onset of PD. Misu and Goshima proved that L-dopa itself can be a biologically active substance, such as a neurotransmitter or neuromodulator and can stimulate DA neurotransmission[54]. Thus, L-dopa itself could play a role in the genesis of dyskinesias in patients receiving chronic L-dopa therapy.

Fear of levodopa neurotoxicity

High concentrations of levodopa used in DA cell culture systems have been reported to be toxic, especially since L-dopa is easily oxidized non-enzymatically, producing highly reactive metabolites thought to attack subcellular organelles and cell membranes of DA neurons[55]. Even the development of motor complications has been interpreted as a toxic effect of levodopa, not a side effect of its long-term use. However, clinical evidence suggests the opposite[56]. The idea that L-dopa is not neurotoxic enough to cause DA neuron degeneration, is supported by the fact that long-term use of the drug in dopa-reactive dystonia (Segawa's disease) does not cause unwanted effects. Segawa's disease occurs as a consequence of the lack tetrahydrobiopterin (BH4) as a cofactor required for TH activity, resulting in a decrease in dopamine concentration, especially in nigrostriatal DA neurons[57]. However, unlike Segawa's disease, in which DA neurons do not die, DA neurons slowly but progressively degenerate in PD, and L-dopa is unable to protect them from progressive neurodegeneration.

In the ELLDOPA study, the Parkinson Study Group reported that L-dopa significantly reduced the worsening of symptoms, measured by appropriate scales compared with placebo after 42 weeks of study. The ELLDOPA study compared levodopa doses of 150 mg, 300 mg, and 600 mg, versus placebo in patients with very early PD. This study provides confirmatory evidence for the functional protective effect of L-dopa. Moreover, using predictive models to help distinguish symptomatic from protective effects, Halford et al. obtained evidence for slowing of disease progression using L-dopa/carbidopa as well as some DA agonists (bromocriptine and pergolide)[58].

Levodopa today

The basic assumptions about the occurrence of therapeutic complications are still related to the pharmacokinetics of levodopa and the model of its delivery to the brain, which results in non-physiological, pulsatile stimulation of dopamine receptors[59]. Can continuous stimulation be achieved under conditions of standard, regular patient therapy? The half-life of levodopa makes continuous delivery difficult, when the drug is given orally. In such situations, with the aim of maintaining continuous dopaminergic stimulation, the following are recommended:

a) change in the principle of its application (preparations with continuous release, continuous application of levodopa through a duodenal tube); new formulations of levodopa are designed to improve its delivery and make the stimulation of dopamine receptors more prolonged and physiological

b) application of levodopa degradation enzyme blockers that would ensure its longer survival in the circulation

Table 2. New levodopa preparations

Levodopa accordion pill (AP-LD/CD, Intec pharm), at the research stage	a combination of levodopa and carbidopa with immediate and controlled release, made in the form of capsules made of biodegradable multi-layer films that enable retention in the stomach and gradual release with increased absorption of the drug; superiority of the drug: taking the drug twice a day, but no superiority over the immediate-release drug has been demonstrated
Subcutaneous levodopa (ND0612 NeuroDerm), research is ongoing	a liquid form of LD/CD administered subcutaneously via a small patch pump that would maintain levodopa plasma levels for 24 hours; the dose of the drug given in this way requires additional oral therapy, and the injection sites react with the appearance of erythema and skin nodules
Inhaled levodopa (CVT 301, Acorda Therapeutics)	preparation for individual use, inhalation powder added to regular oral therapy; parallel sc apomorphine (rescue therapy) (registered in the USA, in the process of re-registration in the EU).

Changing the principles of levodopa administration and the application of enzymes for their degradation

A preparation with controlled release

Levodopa with controlled release was made in the form of a hydrodynamically balanced system in which the gelatin capsules dissolve after coming into contact with the gas liquid[60]. This drug was registered in Europe. In the USA, capsules with extended release are also in use, which are designed so that the capsule has a compartment for a preparation with extended release and a preparation with immediate release, which enables longer retention of the drug in the stomach.

Some of the drugs that are in the phase of research or registration are shown in table 2. These are the forms in which levodopa is delivered *per os* or non-enterally (by inhalation, subcutaneously). Although the level of the drug is more stable with their application, they did not solve the problem of motor complications, except for night wearing off, for which forms of levodopa with controlled release are used. Due to the way of delivery (inhalation) and speed of action, some of the studied preparations were aimed at solving sudden offs according to the subcutaneous apomorphine model, but there was no direct comparison between the preparations, so the advantages of the inhaled form of levodopa compared to subcutaneous apomorphine remained unclear.

Intestinal gel (LCIG)

Levodopa-carbidopa intestinal gel (ES) is a carboxy/methyl/cellulose gel that is released continuously into the proximal jejunum via a percutaneous gastrojejunostomy connected to a portable infusion pump. Pharmacokinetic studies show that jejunal infusion of levodopa/carbidopa intestinal gel provides an almost constant plasma concentration of levodopa with less variation, compared to oral preparations[61]. Reducing the fluctuation of levodopa plasma concentrations reduces the fluctuation of the therapeutic response.

The short-term efficacy (12 weeks) of levodopa/carbidopa enteral suspension in patients with advanced PD and motor complications was investigated in two identical randomized double-blind multicenter studies with LCGI. The first was published in 2014[62], and the second in 2016[63]. In both studies, patients with levodopa-carbidopa enteral suspension (ES) had a statistically significant shortening of the off period, as well as a prolongation of the on time without disabling dyskinesias, while the time with disabling dyskinesias as well as the on time with dyskinesias did not increase statistically significantly.

Long-term (up to 7 years) efficacy studies from an open-label, multinational phase III study[64-66] and safety[67] also showed that the positive effect was maintained during the follow-up period. Interestingly, it has been shown that this form of therapy can help reducing non-motor symptoms of the disease, when their presence is an expression of the shortening of the effect of a single dose of the drug (wearing off)[68]. A retrospective analysis, which followed the patients for 3.5 years, showed that only 22% of the patients had frizz compared to 46% at the baseline visit[69]. Improvement of walk disorders (freezing, festination and postural stability) was also shown in 61.4% of patients after 18 months of follow-up[70].

In terms of side effects, ES caused some unwanted effects that were related to the device itself and its installation, and they account for 76% of all complications (abdominal pain, complications after insertion of the product, formation of granular tissue, erythema at the incision site, wound infection, pain and insertion site reaction). They are most often manifested by abdominal pain in 36% and problems related to tube insertion in 41% cases[71].

Polyneuropathies may also occur in 5.3 to 28% of those treated[72], and it has been shown that people receiving B vitamin supplementation have a lower frequency of polyneuropathies[73]. Loss of TT has been described, although long-term, follow-up shows that side effects decrease over time66. Other studies claim that the loss of TT is seen in a high percentage of patients (60%) and it claims, that it correlates with the time the patient spends with dyskinesias in the waking part of the day. Regardless of the degree of weight loss, nutritional status correlates with a higher levodopa equivalent dose (LEDD) as well as with the severity and progression of the disease, and the presence of dysphagia[74].

Conclusion

The position of levodopa is dictated by the knowledge of the level of evidence for the effectiveness of levodopa as the best symptomatic drug in the treatment of PD. The choice of drugs depends on the needs of the patient, who refer to levodopa in case of need for good symptomatic control[75].

It is expected that L-dopa will remain the "gold standard" for the treatment of PD at least until the development of more potent and safer DA agonists or the development of neuroprotective or neurorestorative therapy. Since L-dopa is the best available drug for PD, currently one important approach would be to develop a neuroprotective strategy to prevent the progression of PD with minimal doses of L-dopa that may have less potential to develop side effects at such doses.

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