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Therapy of Parkinson‘s disease

INTRODUCTORY REMARKS

The treatment of Parkinson‘s disease begins quite differently from the usual approach. The conversation with the affected person and their accompanying and caring relatives marks the beginning of the treatment. The first few minutes around the diagnostic report are crucial for a good and prosperous joint work on and with this disease.

The therapeutic possibilities available to us today enable us to cope well with the motor symptoms of Parkinson‘s disease for years to come and also in the late stage there are methods available that have taken the fear out of the disease. In addition to tablets as the usual dosage form, surgery, plasters, and pump systems have been added.

Deep brain stimulation is now a well-established method. At the most advanced centers, it is already performed under general anesthesia, which also increases comfort of the treatment.

The necessity of the „third pillar of therapy“ with movement therapy, physiotherapy, occupational therapy, logopaedic treatments, as well as the psychological care of those affected and their relatives or the combination of these measures in climate and experience therapy are an integral part of the overall treatment concept. (Figure 1)

Figure 1

Climate and experience therapy of M. Parkinson‘s disease

Tai Chi at the Dead Sea

THERAPEUTIC POSSIBILITIES

Dopaminergic Therapies

The key question in the optimization of dopamine replacement in Parkinson‘s disease is, therefore, how physiological continuous dopaminergic stimulation could be induced, as there are several possibilities for alleviating motor fluctuations.

- Early use or addition of dopamine agonists
- Dose fractionation (= more frequent administration of lower doses)
- Use of L-dopa in retard formulation
- Addition of a COMT-inhibitor
- Addition of an MAO-B-inhibitor

Dopa long-term syndrome and CDS (continuous dopaminergic stimulation)

The principle of continuous dopaminergic stimulation aims at the uniform effect of the drugs in the body; today it is assumed that a pulsatile, i.e. constantly fluctuating amount of medication can have an unfavorable effect on the course of the disease and lead to long-term side effects. For this reason, the right therapy is a declared goal of treatment even in the early stages.

Problems in drug therapy arise over time due to the progression of the disease, which initially requires higher doses of drugs and shorter intervals between taking them. In many cases, complications occur. The capacity of the presynaptic dopamine granules (storage of the carrier substance at the nerve cell endings, where they wait to be released by the nerve impulse) has then decreased so much that they can no longer store enough dopamine to release it when needed. The dopamine is released involuntarily and the duration of the drug‘s effect on mobility and other symptoms is thereby shortened. Conventional therapy very often results in the therapeutic effect being undershot or exceeded to an unpredictable extent („ON/OFF“-symptoms). The consequences are stiffness or lack of mobility (dys-/hyperkinesia) and cramps (dystonia). Over time, the storage capacity decreases further and the symptoms worsen.

In recent years, attempts have been made to find an acceptable solution with continuous dopaminergic stimulation. Dopamine agonists stimulate the receptors evenly, levodopa in more frequent doses and low single doses and if necessary with the addition of COMT- and MAO-B-inhibitors is often a very effective treatment regime. Unfortunately, there are still some patients who are practically unable to be treated with oral medication. Some of them are also no longer suitable for DBS (deep brain stimulation).

Fluctuations (fluctuations in effectiveness) and dyskinesias (involuntary movements) can only be controlled to a limited extent, even with a carefully coordinated combination therapy with dopamine agonists and/or a COMT-inhibitor in addition to levodopa as well as by six to ten single doses per day. At an advanced stage, the patient‘s mobility is therefore often bought at the price of additional dyskinesias, or states of good (ON) and poor (OFF) mobility alternate.

DOPA and COMT-inhibitors

In combination preparations, the effective levodopa and two enzymes that prevent degradation are combined in one pill. Levodopa can cross the blood-brain barrier, the two inhibitors carbidopa (DDC-I – dopa-decarboxylase-inhibitor) and entacapone (COMT-I – catecholamine-O-methyl-transferase inhibitor) are only active before it, i.e. in the blood circulation. This leads to higher availability of DOPA over a longer period of time. It is therefore a stabilized DOPA effect, but contrary to frequent opinion, this triple combination does not replace the effect of dopamine agonists or MAO-B-inhibitors.

Dopamine agonists

Dopamine agonists sensitize the effect location (receptor) for the dopamine and thus lead to a longer, more stable and stronger effect of the drug L-Dopa. There are two groups, the older ergoline substances bromocriptine, lisuride, pergolide, and cabergoline are no longer used because of their side effects. The non-ergoline dopamine agonists Pramipexol and Ropinirole are also available in retard form and only need to be given once a day. This leads to a more constant effective level in the sense of CDS and better control of intake. The dopamine agonist rotigotine, which is also not ergoline, is applied via a transdermal system. This patch, which is stuck to the skin, works constantly over 24 hours due to the even release of the active ingredient (Figure 2). It also has a favorable side-effect profile and can be applied at any time of the day.

Figure 2

The Rotigotine Pavement

Good adhesion on the skin, which enables a direct transfer of the substance

Dopamine agonists were predominantly used in combination with L-dopa, both in the early stages and in the advanced stages of the disease. Dopamine agonists have become the first-choice monotherapy, especially for younger patients in the early stages of the disease. The dosage should creep in and the side effect profile should be pointed out. Only when, after a few years, the effect is really no longer sufficient, it is combined with L-dopa.

Initial monotherapy

Dopamine agonist monotherapy is associated with a significantly lower incidence of dyskinesia. This advantage not only exists for pure monotherapy, but also remains after an additional therapy with L-dopa. The motor efficacy of monotherapy with the subsequent addition of L-dopa is practically equivalent to that of L-dopa monotherapy over the 5-year period investigated.

Combination therapy with L-dopa

With the dopamine agonists, the possibility of combination therapy is furthermore retained. This is particularly useful if fluctuations in efficacy and dyskinesias have occurred during an L-dopa therapy that has been in place for years. Here one can work towards a dopa dose reduction and hope for a decrease of the ON/OFF-phenomena and a prolongation of the ON-period.

MAO-B-inhibitor

Rasagiline is a potent, irreversible selective MAO-B-inhibitor. It is approved for the treatment of idiopathic Parkinson‘s disease as a monotherapy (without levodopa) or as an adjunct therapy (with levodopa) in patients with end-of-dose fluctuations and dyskinesia but is also indicated at the earliest stages of the disease. Fluctuations are shortened by rasagiline. It can be given from the beginning in a fixed once daily dose of 1 mg. The unwanted amphetamine metabolites observed in previous MAO-B-inhibitors do not occur, so no adverse effects on night sleep are expected.

It is the only substance for which not only a symptomatic effect has been proven, but also a certain influence on the course of the disease in long-term studies. Even after six years, the group of people previously treated with rasagiline is still slightly better than those who received rasagiline six months later.

Anti-Glutamatergic Therapies

Glutamate is a brain-stimulating neurotransmitter and the antagonist of dopamine. The inhibition of glutamate leads to an improvement of the symptoms because the due to the dopamine deficiency relatively increased glutamate level is thus brought back into balance.

Amantadine

Glutamate antagonism is caused by a receptor blockade of the NMDA receptor. Amantadine is effective in the early stage of mild symptoms, whereby the rapid effect on all cardinal symptoms should be mentioned here, although tremor also has a particularly good response, fortunately, because in contrast to Akinesia and rigor tremor responds poorly to pure dopa substitution.

The use as monotherapy at the beginning is possible, but often a combination therapy is chosen.

In addition to the therapy in the early stages, the administration in late stages is also important, as amantadine can very well alleviate the dyskinesias, which can otherwise only be achieved by reducing the dopaminergic therapy, but mostly at the cost of symptom accentuation. This antidyskinetic effect persists even after a follow-up check after more than one year, so there is no loss of efficacy. The symptom of wearing-off, which often accompanies dyskinesia, is also a good indication for the substance.

Under dopaminergic therapy, akinetic crises are observed in addition to fluctuations in efficacy. Here the classic use of amantadine as infusion therapy is given since a rapid effect is sought to end the condition, but oral administration is also not possible at all. The situation is similar for patients with swallowing disorders and during perioperative periods when oral therapies cannot be used for various surgical reasons. Amantadine also has a very beneficial effect on persisting salivary flow without causing a massive dry mouth, as is the case when anticholinergic substances are used.

Special therapies in the late stage

Apomorphine

(Figure 3)

Apomorphine is a highly potent non-specific dopamine agonist. This subcutaneously injected substance has been successfully used in England for many years. In the mid-1980s an attempt was made to revive the therapy, but this failed due to inadequate infusion technology and the lack of a suitable and approved apomorphine. The application in sudden OFF-periods takes place by means of pen injection with a response in a few minutes' time (Figure 1), the effect lasts about one hour.

Only the application of the APO-go apomorphine ampoules in pen form and the APO-go Crono pump made it possible to standardize the therapy for the first time in order to make it simple and practicable again for patients. The indication is the late stage of Parkinson's disease, in which sufficient therapy with standard medication alone can no longer be achieved.

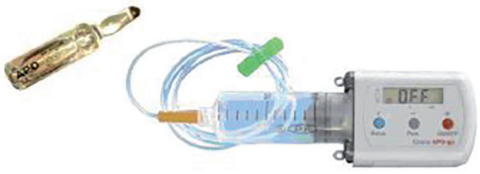


Figure 3

Apo-Go chrono pump

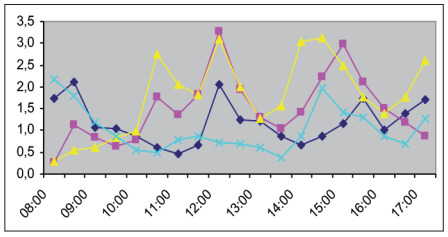
The dopamine agonist apomorphine is continuously applied subcutaneously via a small pump.

LCIG (duodenal DOPA infusion)

For patients who have undergone oral therapy, however, there is another practical solution: an automatic, parenteral treatment system for doping administration (LCIG - levodopa/carbidopa gastrointestinal gel). By providing continuous and uniform dopamine substitution directly into the small intestine, patients can move normally again. (Figure 5) With the help of an externally carried pump, the medication is supplied to the intestine via a probe (the usual PEG probe is equipped with an additional tube (PEJ probe) which is placed in the small intestine, the puncture site is the same as with the conventional PEG probe and has only 2 lumens). In this way, an even flow of dopamine is achieved, independent of gastric emptying. The positive therapeutic effects have been proven in numerous studies. In a randomized crossover study, 24 patients with severe hyperkinetic fluctuations were each treated with the new therapy concept for three weeks. In these patients, the time of largely normal mobility increased by 81 to 100 percent.

LCIG (levodopa and the decarboxylase inhibitor carbidopa in a ratio of 4:1) reaches the small intestine directly via the probe, where levodopa is very quickly absorbed by a high-performance transport system for amino acids. The direct intestinal bioavailability corresponds to that of the tablets. Thanks to the elimination of the gastric passage with its intermittent emptying of the stomach, the fluctuations of the plasma levels (Figure 4) are considerably lower in the individual patient. The more even blood levels thus achieved improve motor fluctuations and prolong ON-periods. Despite continued treatment, not only is there no evidence of a tolerance phenomenon, but the levodopa dose can even be reduced while clinical efficacy remains the same.

Oral DOPA



duodopa

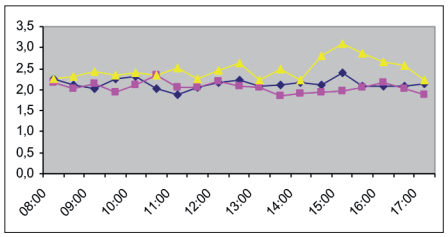


Figure 4

Plasma levels of DOPA

with different forms of application on the same patient

The advantage of LCIG therapy is that very stable blood and thus brain concentration of L-dopa is achieved. As a result, the fluctuations in effect frequently observed with other Parkinson‘s drugs disappear, and patients have good mobility for a considerably greater part of the day without over-movement.

Duodopa proves once again that levodopa, the substance first used in Vienna more than 50 years ago, still has its significance and remains an indispensable component of our therapy concepts.

Figure 5

Duodopa pump

DBS – deep brain stimulation, Tiefe Hirnstimulation

(Figure 6)

In 1990, the French neurosurgeon Alim Louis Benabid performed deep brain stimulation for the treatment of Parkinson‘s disease for the first time. The high effectiveness of the method quickly led to its global popularity. In the meantime, surgery has become an integral part of the spectrum of possibilities in the treatment of Parkinson‘s disease. The implantation technique and the electrodes have been continuously refined in recent years.

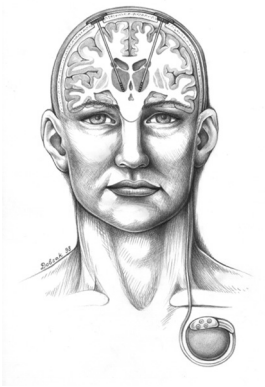


Figure 6

Deep brain stimulation

Electrical stimulation is carried out predominantly in the subthalamic nucleus via electrodes implanted on both sides. The stimulator as well as the connecting cables are implanted completely subcutaneously. The parameters of the stimulation can be changed with external control units.

Imaging techniques, especially magnetic resonance imaging and image fusion between magnetic resonance and computer tomography, have been used more and more in surgical planning. New devices with a particularly strong magnetic field (3 Tesla) deliver images of outstanding quality and sharpness. Physiological methods such as microelectrode derivation, i.e. the derivation of brain currents from the affected brain areas during surgery, have also further improved (hit)-safety. These improvements in microelectronics, along with the target-„maps“ obtained from the stored data of many patients, now make it possible to dispense with the active assistance of the patient during the surgery and thus their alertness.

Hence nothing stood in the way of anesthesia for the entire duration of the surgery.

For many years, deep brain stimulation procedures have been performed in our group under general anesthesia. The functional results have essentially remained the same, and the strain on the patients has thus decreased significantly. It is now also possible to operate on patients for whom the surgery has previously not been possible for health or age reasons. By using a special technique, this type of anesthesia is also well tolerated by Parkinson‘s patients.

DBS - Deep Brain Stimulation

Inclusion criteria

- Patients with idiopathic Parkinson‘s disease and excellent response to L-dopa
- Hoehn and Yahr stage in ON not worse than III
- Effect Fluctuations and L-Dopa Induced Dyskinesias
- Therapy refractory tremor

DBS - Deep Brain Stimulation

Exclusion criteria

- Dementia: MMSE < 24 points/DSM IV criteria
- Major depression with acute suicidal tendency
- Severe personality/behavioral disorder (homeostatic hedonistic dysregulation)
- Non-IPS
- Structural brain lesions: brain atrophy, hydrocephalus, hypertensive vasculopathy, tumor, malformations, AV-malformations, aneurysms
- Internal contraindications

CONCLUDING REMARK

Nothing is as interesting as sensations and news. This is true for gene therapy as well as for nanotechnology and other „spacy“ innovations in the virtual world. In reality, these ideas often fail for years. Not that there is no progress and that it isn‘t included in the concepts of the newer treatment methods! In recent years, various Parkin-genes have been discovered and the protein alpha-synuclein has become the focus of interest. So you have to forget the idea that there is a genetic alteration that would trigger Parkinson‘s – the opposite has already been proven. In contrast to sporadic cases, the number of Parkinson‘s families is very limited. In fact, we have more married couples with Parkinson‘s than parents/children or siblings. Here environmental factors seem to have a greater influence, direct inheritance takes a back seat.

Parkinson‘s disease is a neurodegenerative disease. It is to be expected that in a few years the disease process can be stopped, neuroprotective (nerve cell protecting) therapy possibilities will come, but neurorestorative (nerve cell restoring) approaches keep us waiting. However, it has always been the case that one development leads to another. The more disease-delaying possibilities there will be, the more important early detection will become, projects that are currently being intensively worked on away from the sensations. Because the earlier we recognize the approach of neurodegeneration, the more functioning nerve cells we can still protect and the less disability those affected develop over time. We have known for some time that odor and taste disorders precede motor complaints, that vegetative disorders (drop in blood pressure when getting up, certain changes in sleep profile, constipation, erectile dysfunction) also begin before the first signs of Parkinson‘s syndrome.

Every chronically ill person is looking for a cure. In the case of neurodegenerative diseases, we will probably have to exercise patience for some time. However, we have an arsenal of symptomatically effective and partly also neuroprotective drugs at our disposal, which should be used sensibly. With a good selection of patients, these new methods will be a great gain in quality of life and joie de vivre for a certain number of people. This should also be the aim of the therapy because the adaptation of life expectancy to that of the „normal population“ of the same age

was already successful with the introduction of the DOPA therapy by Birkmayer and Hornykiewicz in 1961.

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