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Modern therapy of Parkinson's disease

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Summary. The article summarizes historical aspects and current concepts of the treatment of Parkinson's disease. Antiparkinsonian therapy varies with the progression of the disease, age and clinical subtypes. Levodopa, anticholinergic substances, direct dopamine agonists, amantadine, L-deprenyl are used to treat motor symptoms of Parkinson's disease. Novel substances and therapeutic concepts are currently investigated. Treatment of non-motor symptoms of Parkinson's disease and supportive therapies are discussed in the article.

Introduction

The clinical characteristics of Parkinson's disease are rigidity, bradykinesia, tremor at rest, dysarthria as well as impairment of gait, posture and axial movements. In addition, hypersalivation, hyperhidrosis, seborrhea, orthostatic hypotension, constipation, bladder dysfunction, impairment of convergence, depression and deficits of cognitive and mnestic functions are observed in Parkinson's disease (Parkinson, 1817; Duvoisin, 1984; Ward and Gibb, 1990). The neuropathological hallmarks of the disease are a decrease of dopaminergic neurons in the substantia nigra pars compacta and the Lewy body, an intracytoplasmatic inclusion body located in aminergic and cholinergic nuclei of the brainstem, the diencephalon, the basal forebrain and in the cortex (Jellinger, 1986). Furthermore, significant impairments of neurons, neurotransmitters and neurotransmitter – synthesizing enzymes are found in noradrenergic, serotoninergic, cholinergic, glutamatergic and neuropeptidergic systems of the brainstem, the diencephalon, the basal forebrain and the cortex (Hornykiewicz et al., 1986; Agid et al., 1990).

In the last century natural belladonna alkaloids were introduced to treat parkinsonian motor symptoms (Charcot, 1877). The first synthetic substances used for the treatment of Parkinson's disease were anticholinergics (Cunningham et al., 1949). In 1958 Carlsson et al. described the localization of catecholamines in the central nervous system and discussed their roles in physiological processes (Carlsson et al., 1958; Carlsson, 1959). In 1960

Ehringer and Hornykiewicz found a significant loss of dopamine in the brains of patients with Parkinson's disease (Ehringer and Hornykiewicz, 1960) and, thus, the basis of levodopa therapy which, one year later, was found to be effective against akinesia and rigidity (Birkmayer and Hornykiewicz, 1961; Barbeau et al., 1961). In 1962 the anti-rigidity effect of levodopa was electromyographically verified (Gerstenbrand and Pateisky, 1962) and a variable effect of levodopa on tremor reported (Gerstenbrand et al., 1963).

Since the seventies direct dopamine agonists, above all synthetic ergot alkaloid derivatives have been introduced to treat parkinsonian motor symptoms and to alleviate motor-fluctuations observed under long-term oral levodopa therapy (Calne et al., 1974; Lees et al., 1978; Lieberman et al., 1981; Parkes et al., 1981; Tanner et al., 1986; Sage et al., 1989; Horowski and Obeso, 1990). The MAO-B-inhibitor L-deprenyl was shown to enhance the effect of levodopa and to slow down the progression of the disease (Birkmayer et al., 1977, 1985; Tetrud and Langston, 1989; The Parkinson Study Group, 1989; Rinne et al., 1991). Further innovations in modern antiparkinsonian therapy in patients with motor-fluctuations were the parenteral administration of antiparkinsonian substances, such as levodopa (Shoulsen et al., 1975; Mouradian et al., 1990), lisuride (Obeso et al., 1986; Ruggieri et al., 1986) and apomorphine (Schwab et al., 1951; Corsini et al., 1979; Stibe et al., 1988), and the grafting of adrenal medullary and fetal mesencephalic tissue to the basal ganglia (Björklund et al., 1980; Backlund et al., 1985; Madrazo et al., 1987; Lindvall et al., 1992). Recently, a glutamatergic preponderence was found in the subthalamic nucleus of parkinsonian patients and its therapeutic implications in Parkinson's disease are currently under investigation (Kornhuber et al., 1989; Aziz et al., 1991; Klockgether et al., 1991). New dopamine agonists, such as cabergoline and ropirinole (Jori et al., 1990; Vidailhet et al., 1990), the partial dopamine agonist and antagonist terguride (Brücke et al., 1986), a catechol-O methyl-transferase inhibitor (Da Prada et al., 1991) and neuropeptidergic substances, such as the tripeptides MIF (Kastin and Barbeau, 1972; Fischer et al., 1974; Barbeau, 1975; Gerstenbrand et al., 1975, 1979) and doreptide (Gerstenbrand et al., in preparation) have been tested in preclinical and clinical trials and it seems as if some of them would be useful in the treatment of early and advanced Parkinson's disease.

Treatment of early Parkinson's disease (stage of stable response to treatment)

The early stage of Parkinson's disease is characterized by mild motor symptoms (tremor at rest, rigidity, bradykinesia, mild axial motor impairment) responding well to antiparkinsonian therapy. Peroral amantadine (sulphate or hydrochloride) 100 mg tds (Schwab et al., 1969), L-deprenyl 5 mg twice daily (Birkmayer et al., 1977), and anticholinergic substances (benztropine, trihexiphenidyl or biperiden, 2–4 mg tds) may alleviate parkinsonian motor symptoms for a period

of several months to few years. The pharmacological basis of anticholinergic therapy is an inhibition of cholinergic striatal interneurons which are disinhibited due to the loss of dopaminergic input from the substantia nigra pars compacta (Duvoisin, 1966). Amantadin is a dopaminergic and anti-glutamatergic substance (Kornhuber et al., 1989) and L-deprenyl inhibits MAO-B, an enzyme degrading dopamine (Birkmayer et al., 1977). With increasing duration of the disease dopaminergic substances, such as levodopa and direct dopamine receptor agonists become indispensable. Oral levodopa combined with a peripherally acting decarboxylase inhibitor (benserazide 4:1 or carbidopa 10:1 or 1:4) is the golden standard of antiparkinsonian therapy (150–800 mg levodopa, given in three to four daily doses). The optimum daily dosage may vary between patients. Levodopa alleviates bradykinesia, rigidity, axial motor symptoms and tremor and may also diminish mental slowing and depression. The substance is well characterized with regard to its efficacy and acute (hyperkinesias, sometimes nausea and orthostatic hypotension, psychotic episodes in elderly or demented parkinsonian patients) and chronic side-effects (see below). Levodopa is a well characterized potent substance for the treatment of Parkinson's disease.

Levodopa should not be withheld for fear of motor response fluctuations (delayed onset and decreasing duration of the therapeutic effect of single levodopa doses, peak-dose or onset- and end-of-dose choreic or dystonic dyskinesias, myoclonus and unpredictable "off" and "on" states; Agid et al., 1985). The occurence of levodopa induced motor fluctuations (see below) is related to the severity of the motor symptoms rigidity and bradykinesia and the duration of the disease. Furthermore, motor response fluctuations occur earlier in younger than in older patients (Markham and Diamond, 1981; Pederzoli et al., 1983; Quinn et al., 1986; Cedarbaum, 1987; Horstink et al., 1990). Levodopa may be combined with L-deprenyl (10 mg daily) as L-deprenyl is supposed to exert a decelerating effect on the progression of Parkinson's disease (Birkmayer et al., 1985; The Parkinson Study Group, 1989; Tetrud and Langston, 1989; Rinne et al., 1991). In general L-deprenyl is well tolerated. Only a minority of patients reports gastric discomfort under L-deprenyl treatment.

The potency of levodopa to alleviate motor symptoms, in particular axial symptoms, decreases with increasing age and duration of the disease (Ransmayr et al., 1992). Nevertheless, levodopa improves markedly the quality of life and does not accelerate the progression of Parkinson's disease (Blin et al., 1988).

Therapy of advanced Parkinson's disease (stage of predictable motor fluctuations)

After several years of levodopa therapy duration of the efficacy of the single levodopa dosages decreases (end-of-dose deterioration). To avoid periodic deterioration of parkinsonian motor symptoms and peak-dose effects (peak-

dose dyskinesias) the daily dosage should be maintained unchanged or increased and fractionated (6–10 instead of 3–4 daily doses) (Mouradian et al., 1989). L-deprenyl is sometimes effective in mild end-of-dose deterioration (Schachter et al., 1980). Meals rich in proteins deteriorate the resorption of levodopa from the small intestine and the transport of levodopa through the blood-brain barrier (Juncos et al., 1987; Pincus and Barry, 1988; Tsui et al., 1989). Slowing of gastric emptying may also contribute to a loss of efficacy of levodopa therapy (Kurlan, 1988 a). In mild cases domperidone may be useful to accelerate gastric emptying (Baas et al., 1991). Some authors recommend continuous enteral infusions of levodopa via a duodenal catheter (Kurlan et al., 1988; Sage et al., 1988, 1989).

Slow-release preparations of levodopa plus decarboxylase inhibitor (Madopar-HBS, Sinemet-CR) may improve motor-fluctuations, in particular in patients with narrow therapeutic ranges between peak-dose dyskinesias and "off"-states. The slow-release preparations are above all useful against nocturnal akinesia and foot cramps (100–300 mg slow-release levodopa at night; Nutt et al., 1986; Poewe et al., 1989; Rinne and Rinne, 1989). Fluctuations of the levodopa plasma level and pharmacodynamic factors play an increasing role in the failure of chronic levodopa therapy with progression of the disease (Fabbrini et al., 1987; Kempster et al., 1989). Substances with longer bioavailability than oral levodopa and direct dopamine receptor-agonist effect, such as bromocriptine, pergolide or lisuride are given in combination with levodopa or as alternatives to levodopa. Early combination of levodopa with dopamine-agonists or monotherapy with dopamine-agonists reduce significantly incidence and severity of motor response fluctuations (Calne et al., 1978; Fischer et al., 1984; Rinne, 1987). Dopamine-agonists are sometimes only effective in combination with levodopa. Nausea, orthostatic hypotension, hyperkinesias, sedation, impairment of sleep, psychotic episodes (preponderantly in elderly and demented patients) may occur under dopamine-agonist treatment. The daily dosages of dopamine-agonists should be slowly increased to avoid or minimize side-effects. Previous and concomitant treatment with domperidone (20 mg tds) prevents or reduces nausea (Parkes, 1986). Long-term treatment with dopamine-agonists may cause pleuropulmonary fibrosis, gain of weight, swelling of the feet, hypersexuality or impotence, elevation of liver enzymes (pergolide) and peripheral angiospasm (Bhatt et al., 1991). Therefore, patients on dopamine-agonists should be followed at regular intervals.

Therapy of late stages of Parkinson's disease (stage of unpredictable motor fluctuations)

In late stages of Parkinson's disease motor response fluctuations occur abruptly and at varying time-points. Such fluctuations are more or less uncontrollable with oral antiparkinsonian therapy. Continuous intravenous ad-

ministration of levodopa (Shoulsen et al., 1975) or levodopa methyl-ester (Cooper et al., 1984) improve frequency and severity of motor response fluctuations. Apomorphine is a potent substance for the treatment of unpredictable motor-fluctuations. In patients with rare "off"-phases or foot cramps the substance is given in single doses subcutaneously (4–8 mg) by means of a penject, intranasally (<8 mg) or sublingually (30 mg; Corsini et al., 1979; Stibe et al., 1988; Poewe et al., 1988; Lees et al., 1991; Kapoor et al., 1991; Kleedorfer et al., 1991). In the case of severe motor fluctuations apomorphine is continuously administered into the subcutis over twelve to twenty-four hours daily with an extracorporal pump (4–10 mg per hour). The side effects of apomorphine are similar to those of other dopamine-agonists. To avoid nausea patients are treated with domperidone (20–30 mg tds) during the first weeks and months of apomorphine therapy. Local irritations may occur at the injection site and at the nasal mucosa and autoimmune hemolytic amemia occurred in a few patients receiving apomorphine therapy.

Lisuride was found to be more effective against unpredictable motor-fluctuations when it is administered intravenously or subcutaneously instead of orally (Obeso et al., 1986; Ruggieri et al., 1986; Horowski and Obeso, 1990). In elderly parkinsonian patients not tolerating levodopa or dopaminomimetic therapy intravenous infusions of amantadine (100–200 mg daily) may help to overcome akinetic states. In elderlies confusion and peripheral edema may occur under amantadine. In patients with severe Parkinson's disease L-threo-DOPS was described to alleviate axial motor symptoms (Reches, 1985). The efficacy of the substance not yet established.

Treatment of parkinsonian tremor

The classical parkinsonian tremor is a 4–7/sec. somewhat assymmetrical tremor at rest, which in a minority of patients may be combined with action tremor. Tremor at rest responds to levodopa, dopamine-agonists, anticholinergic substances, such as trihexiphenidyl, biperiden, benztropine (2–4 mg tds) and budipine (30–60 mg daily; Poewe et al., 1985; Jellinger and Bliesath, 1987; LeWitt and Truong, 1990). Propranolol (10–20 mg tds; Abramsky et al., 1971) and bupranolol (Gerstenbrand et al., 1978) are also effective against parkinsonian tremor, in particular against action tremor. Clozapine has recently demonstrated to reduce parkinsonian tremor (Fischer et al., 1991). Anticholinergic substances should not be used in patients with dementia and history of psychotic episodes, narrow angle glaucoma, constipation and urinary retention due to disorders of the prostate. Beta-blockers should not be prescribed in patients with orthostatic hypotension, pulmonary and certain cardiac disorders, diabetes and peripheral circulatory disturbances. Clozapine may cause leucopenia. Therefore, the peripheral leucocyte counts have to be monitored at regular intervals.

Further aspects in the treatment of Parkinson's disease

Three clinical subtypes of Parkinson's disease can be distinguished, the rigidity-akinesia type, the tremor-dominance type and the rigidity-akinesia-tremor type (Poewe et al., 1983). The subtype with the best prognosis as to disability and therapy complications is the tremor-type. In contrast, the rigidity-akinesia type is the subtype with the least favorable prognosis. In the latter subtype higher dosages of levodopa therapy are needed than in the two other subtypes and psychotic episodes are more frequently observed (Ransmayr et al., 1986). Therefore, patients with rigidity-akinesia type tolerate less well dopaminomimetic substances than patients of the two other subtypes.

Anticholinergic substances may alleviate hypersalivation. Laxatives and domperidone may help to alleviate constipation. Urodynamic examinations are required to characterize and treat urinary bladder dysfunction related to Parkinson's disease.

Physical therapy is recommended, in particular in advanced stages of the disease to overcome motor disability resulting from therapy-resistant parkinsonian motor symptoms, such as "axial apraxia" (Lakke, 1985) and imbalance of gait and stance. Patients should learn to improve posture in order to avoid secondary complications of Parkinson's disease, such as cervical spondylosis and myelopathy.

Depression is observed in 15 to 60% of the patients and requires individual therapeutic approaches. In a minority of patients antidepressive therapy with tricyclics is necessary. A substantial proportion of patients improve in parallel to the improvement of the motor impairment under levodopa therapy. Many patients suffer from inner tension and anxiety. Therefore, anxiolytic substances, such as benzodiazepine derivatives are frequently needed.

In the case of psychotic episodes under levodopa, dopamine-agonists or anticholinergics the dosages of these substances have to be reduced. Sometimes atypical neuroleptics, such as clozapine need to be administered (Wolters et al., 1990). However, parkinsonian motor symptoms may aggravate under clozapine treatment. Concomitant treatment with CDP-choline may lead to some improvement of cognitive functions (Eberhardt et al., 1991). In a minority of patients levodopa may improve vigilance.

Conclusions

Symptomatic treatment of Parkinson's disease should start as soon as the patient is impaired in occupational functions and activities of daily living. Therapy with L-deprenyl should be initiated as soon as the diagnosis is established even though the long-term prophylactic effect of L-deprenyl is not yet established. Different phases of Parkinson's disease are distinguished in the course of the disease requiring different therapeutic principles. It is also

important to consider the age of the patients and clinical subtypes of Parkinson's disease in the planning of therapy. Parkinson's disease is a multisystemic disease and for the majority of the involved neurotransmitter systems therapeutic approaches are not yet available. Antiparkinsonian therapy of the future will presumably be multimodal comprising dopaminergic and antiglutamatergic substances and also substances against neuropeptidergic and so far unknown neurotransmitter impairments. Growth factors and the use of new systems of drug dilivery are currently investigated in Parkinson's disease. The role of these methods in the treatment of Parkinson's disease will be established in the near future.

Parkinson's disease is a motor disease associated with a variety of mental symptoms and psychological and social difficulties. It is important to offer the patients not only optimal pharmacotherapy, but also psychological support and guidance, in particular in phases of increasing pharmacotherapeutic difficulties.

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