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Modern Approach to the Treatment of Parkinson's Disease: The Role of Pramipexole In The Correction of Motor and Non-Motor Disorders

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ABSTRACT

Parkinson's disease (PD) is a progressive neurological disorder characterized by a large number of motor and non-motor features that can impact on function to a variable degree. The syndrome of parkinsonism is highlighted, which can become apparent with akinetic rigid disorders in other brain injuries including medication-induced parkinsonism. Genetic mutations or variants, neuroimaging abnormalities and other tests are potential biomarkers that may improve diagnosis and allow the identification of persons at risk. This literature review describes pathogenesis and clinical characteristics of PD with emphasis on modern treatment and possibilities of dopamine agonists, especially pramipexole. During pramipexole treatment of the patients with the early and late stages of PD, we can observe the reduction of expression of cognitive and affective (mood) disorders, the improvement of the quality of life and social functioning.

Keywords: Parkinson's disease, neurodegenerative disease, pramipexole, depression.

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INTRODUCTION

One of the most prevailing and progressive neurodegeneration among the patients of elderly age (1-2% in population older than 65 years) is Parkinson's disease (PD), which represents special interest to modern pharmacotherapy, which is aimed at the uncovering of key pathobiochemical mechanisms of brain's lesion^{1, 2}. The prevalence of its in Zambia is unknown, but it is the third of the most often disease after epilepsy and stroke.

Except PD, which is connected mainly with neurodegeneration, the syndrome of parkinsonism is highlighted, which can become apparent with akinetic rigid disorders in other brain injuries (vascular, toxic, medication induced, posttraumatic and post-encephalitic parkinsonism)^{1, 3}. This article scrutinizes in details the possibilities of dopamine agonists, particularly pramipexole, in modern clinical practice of PD treatment.

Modern Conceptions of Pathogenesis of the Disease

Parkinsonism is known long since, the first information about treatment of such diseases appeared in 2500-100 BC in Ayurveda's lists, which was preserved to the present time, where there were propositions to use the plant *mucuna pruriens*, which consists dopaminergic matter. Some symptoms resembling the display of parkinsonism were described by Galen in II century and Leonardo da Vinci in XV century.

The first clinical description was made by English physician James Parkinson in «An Essay on the Shaking Palsy» published in 1817. Detailed clinical analysis of pathology complex was made in 1879 by French famous neurologist Jean-Martin Charcot. Except the trembling, difficulties with walking and general constraint admitted in due time by J. Parkinson as muscular feebleness. He introduced the concept of bradykinesia and proposed also a new name – Parkinson's disease.

Among the movement disorders in neurology such syndromes are observed: paralysis, paresis, akinetic hypertonic and hyperkinetic hypotonic variants of movement disorders, ataxia, sudden falling and epileptic syndromes. Among them, the part of parkinsonism only akinetic hypertonic variants of movement disorders are due, which contain hypokinesia, muscle rigidity, tremor (especially in quiescent state) and postural disorders. Muscle hypertonia-hypokinesia deprives the patient's possibility of coordinating movements and tremble makes big obstacles of self-care and professional activity.

The symptoms of PD often are not limited only to movement disorders. Vegetative dysfunctions, which are observed in patients with parkinsonism, provoke not minor discomfort and are found very often. Because of complexity of brain's pathobiochemistry, with this disease the dynamic balance is removed to the predominance of parasympathetic tone of autonomic nervous system.

Typical symptoms of parkinsonism are arterial hypotonia and constipation as results of a vegetative dysfunction. Usually movement disorders are accompanied with hyperseborrhea (“oily face”) especially on the forehead, sides of the nose, scalp and eyebrows, hypersalivation (sialorrhoea), arthrosis of fine joints, nails fragility, osteoporosis, weight loss. Disorders of autonomic regulation can be paroxysmal, mainly in the form of vago-insular and mixed crisis, but often there are cases of benign paroxysmal positional vertigo (BPPV), diffuse hyperhidrosis, cardialgia and frequent urination.

Approximately 85% of patients have mental impairments. Often there are the symptoms of depression in such patients ^{2,4}. Expressiveness of motive symptoms is dependent on psychical and emotional state of a patient: tremor increases emotional tension and diminishes at the quiescent state. Slowness of thought (bradyphrenia) in combination with the depression leads to severe impairment of cognitive functions and high risk of developing dementia.

The symptoms associated with PD are presented in the Table 1 and differential diagnostic features of essential tremor and PD are presented in the Table 2.

Table 1: Symptoms associated with Parkinson’s disease

Motor symptoms	Non-motor symptoms
Tremor, bradykinesia, rigidity, postural instability	Cognitive impairment, bradyphrenia, tip-of-the-tongue (word finding) phenomenon
Hypomimia, dysarthria, dysphagia, sialorrhoea	Depression, apathy, anhedonia, fatigue, other behavioural and psychiatric problems
Decreased arm swing, shuffling gait, festination difficulty arising from chair, turning in bed	Sensory symptoms: anosmia, ageusia, pain (shoulder, back), paresthesias
Micrographia, cutting food, feeding, hygiene, slow activities of daily living	Dysautonomia (orthostatic hypotension, constipation, urinary and sexual dysfunction, abnormal sweating, seborrhea), weight loss
Glabellar reflex, blepharospasm, dystonia, striatal deformity, scoliosis, camptocormia	Sleep disorders (REM behaviour disorder, vivid dreams, daytime drowsiness, sleep fragmentation, restless legs syndrome)

Table 2: Features differentiating essential tremor from Parkinson's disease

Feature	Essential tremor	Parkinson's disease
Age at onset (years)	10-80	55-75
Family history	++	+/-
Tremor frequency (Hz)	5-10	4-6
Tremor characteristics	Flexion-extension	Supination-pronation
Influencing factors		
Rest	Decreases	Increases
Action	Increases	Decreases
Mental concentration	Increases	Decreases
Writing	Increases (tremulous)	Decreases (micrographia)
Walking	Decreases	Increases
Alcohol	Decreases	-
Postural tremor	Without latency	Re-emergent
Kinetic tremor	Yes	+/-
Limb tremor	Symmetric	Asymmetric
Distribution other than limbs	Head, voice	Face, jaw, lips, chin
Neuroimaging (dopaminergic system)	Mild dopaminergic deficit	Marked dopaminergic deficit
Mid-brain sonography	Mild hyper-echogenicity	Marked hyper-echogenicity
Neuropathology	Mild cerebellar degeneration, Lewy bodies in the substantia nigra, brainstem and cerebellum some cases	Nigrostriatal degeneration, Lewy bodies
Treatment	Alcohol, beta-blockers, primidone, topiramate, gabapentin, botulinum toxin, deep brain stimulation	Anticholinergics, amantadine, dopaminergic drugs, deep brain stimulation

Principles of Treatment of PD

Degree of severity of the symptoms of PD is directly connected with the level of dopamine in nigrostriatal brain's system and it directly influences the choice of medications. In initial stage of the disease, the deficit of dopamine is expressed marginally, in spite of the degeneration of a significant part of substantia nigra. Preserved cells can provide the adequate level of dopamine through the increase of synthesis and the secretion of dopamine.

This phase of PD can be considered partially compensated, that is why for the treatment we need the medicine normalizing dopamine metabolism. Besides that, we need medicine, which can slack the degeneration of neurons and the progress of disease: so, we need the medicine, which has neuroprotective effects.

It is a general fact, that all the drugs used for PD treatment are labelled as the drugs for symptomatic treatment. Treatment of each patient should be individualized based on the severity of individual symptoms of the disease, the degree of functional maladjustment, age, level of activity of the necessary functionality, as well as the presence of side effects of therapy.

For the patients, younger than 70 years which have the predominance of symptoms of rigidity and akinesia, it is recommended to start the treatment with inhibitor MAO-B – selegiline, amantadine or dopamine agonists (DAs). Anticholinergics are more effective for Idiopathic type of PD predominantly with tremor (tremor type of PD). In complex application of the mentioned medications levodopa is added only when there is no sufficient therapeutic effect. In patients, older than 70 years start of immediate treatment with small dose of levodopa is recommended, as in the elderly, other groups of medications are less effective and often cause somatic and mental side effects.

The Relevance of Neuroprotection in the Treatment of PD

The possibilities of modern neurology in modification of progress of PD, prevention or deceleration of pathological process, prevention of some phases of disease or reverse progression of neurodegenerative changes – all that from clinical positions determine “neuroprotection” remains very confined. The strategy of neuroprotection must be implemented in early or even presynaptic (latent) phase of neurodegenerative process, because of clinical manifestation forms of PD are connected with atrophy of 60 - 80% of dopaminergic nigral neurons and with catastrophic decline of the dopamine level in nigrostriatal dopaminergic neurons and cholinergic nerve endings ⁵. It is actualized the developing of adequate biomarkers of PD – neuroimaging, neurophysiological, biochemical, molecular, genetic and others, which would be informative in early terms of the disease.

Place of Dopamine Agonist in A In the Treatment Of PD

A significant achievement in PD therapy became after widespread use of dopamine agonists (DA). Although this class of antiparkinsonian medications are known since the early 1970s, practical importance is acquired only with the advent of the new generation of drugs such as pramipexole^{6,7,8}.

Results of numerous studies have shown that in the early stages of the disease DAs are capable of a fairly long period of delay prescribing of levodopa and limit its dose^{9,10,11}, in a late - to correct motor fluctuations and dyskinesia^{11,12}.

Pramipexole is highly selective non-ergot dopamine agonist, mainly operating in the D3 subtype of dopamine D2 receptors, is a synthetic amino-benzothiazole derivative. The period of its half-life ranges from 8 hours (young people) and 12 hours (elderly).

Reasonably to start pramipexole therapy with a sub-therapeutic dose (0.125 mg / day), followed by its increase every 5-7 days to achieve personal well-tolerated dose and when we can see the therapeutic effect. In patients with PD pramipexole is effective both as monotherapy and in combination with levodopa.

Combination therapy in most cases can achieve a good result in the appointment of smaller doses, which reduces the potential risk of side effects of each drug. On the other hand, polypharmacology (a combination of three or more pharmaceutical agents) is undesirable because may contribute to the manifestation of side effects.

Levodopa and pramipexole complement each other and are often prescribed together to maximize efficiency and to minimize any side-effects. Perhaps this is due to a short half-life of levodopa, which when used as monotherapy, often provokes dyskinesia and other motor complications.

Pramipexole has a sufficiently long half-life and provides a long-lasting, close to the physiological conditions of DA stimulation, prevents or reduces the expression of developed motor fluctuations and drug-related dyskinesia related to the fluctuations in the level of levodopa concentration in the blood and changes in the sensitivity of dopamine receptors.

New pathophysiological concept suggests that non-physiological stimulation of the dopamine receptors triggers a cascade of new pathological processes: dysregulation of dopaminergic and non-dopaminergic receptors of striatum, the formation of abnormal intracellular pulses in striatal neurons and basal ganglia, which ultimately leads to motor fluctuations and dyskinesia. Pulsatile dopamine receptor stimulation leads to the induction of gene expression of various changes in striatal neurons. This data is the basis for DAs as a first-line therapy in younger patients and elderly patients without decompensated comorbidities.

One of the important argument for the advisability of the beginning of PD therapy with DA is their possible neuroprotective effect. The interaction between genetic and exterior factors is a base of neurodegenerative process in the case of PD. Pathophysiological mechanisms of

neurodegeneration implemented via oxidative stress, formation of free radicals, the development of mitochondrial and proteasomal dysfunction and inflammation.

Efficacy of Pramipexole

According to the latest recommendations of The European Federation of Neurological Societies and European section of the Movement Disorder Society (EFNS / MDS-ES, 2013), the drug of choice must depend on the phase of the disease, the age of a patient, predominant clinical manifestations, level of cognitive functions of the patient, severity of motor disorders with risk of development of motor and neuropsychiatric complications in the background of the prescribed therapy. The authors of the guide recommend pramipexole in oral or transdermal forms for patients in early stage of PD and for patients who previously have not taken other prescribed treatment¹³.

Clinical efficacy of pramipexole was proved through numerous short and long-term randomized double-blind placebo-controlled trials in the treatment of early and advanced stages of PD.

During monotherapy with pramipexole in early stage of PD degree of movement disorders expression has lowered. The score of Unified Parkinson's disease rating scale (UPDRS, part III) was lowering on the average to 25% in comparison with the deterioration to 6,9% in the group of patients, who were taking placebo.

According to EFNS / MDS-ES (2013) recommendations, pramipexole showed to be effective in reducing the duration of the "switched off" period^{11, 13, 14}. It is important to note that when high doses of DA are applied the need for levodopa therapy usually reduced and as a result, dyskinesia decreased¹¹.

In a direct comparison of the effectiveness of pramipexole and levodopa as initial PD therapy (CALM-PD) pramipexole significantly reduced the development of motor fluctuations and medication-induced dyskinesia. Initial pramipexole therapy for 2 and 4 years reduced patient's risk of motor fluctuations in early PD (phenomena of dose response exhaustion and "switching on-off") at 30% compared to levodopa and medication-induced dyskinesia at 50%. However, the overall improvement in the UPDRS scale after 2 years of therapy was more pronounced in the levodopa group, and score on the scale of quality of life did not differ between the two groups.

As a part of the CALM-PD study conducted CALM-PD-CIT substudy using neuroimaging (single photon emission computed tomography), the aim of which was to assess the possible neuroprotective effect of pramipexole. 82 patients of 301 patients were included in the research. They took part in CALM-PD and they were in the early phases of PD. According to the results published in 2002, the percentage of dopamine neurons loss was essentially lower, than in the pramipexole group.

In a double-blind placebo controlled test, where 291 patients were included, the effectiveness of pramipexole by motor fluctuations was evaluated in comparison with placebo ¹². Except the lowering of motor fluctuations, pramipexole demonstrated the effectiveness concerning the duration and the severity of “off-periods” in comparison with placebo, and also allowed to lower the levodopa dose. Documented unwanted side effects did not differ from those of other drugs in this group.

Except the effectiveness in rigidity and akinesia treatment, pramipexole was lowering the expression of tremor, which was demonstrated during the research with the participation of 16 patients with the early phases of PD (11 participants were taking pramipexole, 5 were taking placebo) ¹⁵. The positive dynamics was marked already during the phase of taking 0,75 mg/day (35% had the tremor lowering, 22% had the akinesia lowering according to the UPDRS during “on-periods”). The patients, who were taking 4,5 mg/day, demonstrated 61% of tremor lowering and 65% of rigidity and akinesia lowering. In the ones, who were taking placebo, the improvement of these symptoms was not observed.

The results of research demonstrated, that pramipexole can be useful for the patients in the late phases of PD, helping the lowering of motor fluctuations expressions and dyskinesia expressions ¹⁵. The medicine was giving the most important influence to the phenomenon of exhaustion of the end of dose of levodopa and the dyskinesia of a “off period”. At the same time, the positive influence on the sudden “switching” and other variants of dyskinesia was less stable.

Depression occurs in approximately 40% of patients with the PD and influences negatively on their life quality. Significant advantage of pramipexole, which is also mentioned in the EFNS / MDS-ES manual (2013), is its anti-depressive effect ¹³. In a small study during 8 months was mentioned the reduce of anxiety and depressive symptoms in the course of pergolide and pramipexole ¹⁶. Anti-depressive effect of pramipexole in the cases of PD also was confirmed in the placebo-controlled study, where the improvement was explained by the immediate anti-depressive effect ¹³.

CONCLUSION

In conclusion, it is necessary to mark, that the pramipexole treatment of the patients with the PD ensures very good control of movement disorders, besides the effectivity of the drug is not depended on the stage of disease. Pramipexole influences mainly on the expression of tremor, hypokinesia, rigidity, less postural instability. It also corrects a wide range of neuropsychiatric symptoms of the disease including depression and anxiety.

The correction of different symptoms by using one medicine has the possibility taking into consideration the advantages of the confinement of polypharmacy of PD. Nevertheless, in the case

of necessity of the prescription of pramipexole in combination with others groups of antiparkinson medications, the daily dose of levodopa can be reduced without the loss of pharmacotherapy effects. During the pramipexole treatment of the patients with the early and late stages of PD, we can observe the reduction of expression of cognitive and affective (mood) disorders, the improvement of the quality of life and social functioning.

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