AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 02, Issue 05, 2024 ISSN (E): 2993-2149

PHARMACOTHERAPY FOR PARKINSON'S DISEASE

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Abstract

It is generally accepted that levodopa drugs are the most effective means for the symptomatic treatment of Parkinson's disease (PD). With a long course of PD during therapy with levodopa drugs, the clinical picture of the disease changes (clinical pathomorphosis occurs), levodopa-induced dyskinesias and motor fluctuations occur [1]. Already 2 years after the start of taking dopa-containing drugs, the above complications occur in 50% of patients, and after 10 years - in 80–100%, they become an independent maladaptive factor affecting the daily activity of patients [2]. Levodopa-induced dyskinesias most often manifest in the lower extremities on the side of the body in which the symptoms of PD initially arose and in which the most pronounced manifestations of hypokinesia and rigidity are subsequently noted [3]. Dyskinesia significantly reduces the quality of life of patients, sharply limits their ability to work, and reduces their initiative; patients are forced to change their usual lifestyle. In many patients with PD, due to constant excessive motor activity, body weight decreases, disorders of the cardiovascular system may develop, and generalized hyperhidrosis occurs. In some cases, patients with switch-off dystonias develop a chronic pain syndrome, which may result in the development of affective disorder.

Keywords: To analyze pharmacotherapeutic approaches to the correction of cerebral edema based on the results of our research and analysis of the literature research medications used for Parkinson's disease.

Introduction

It is generally accepted that levodopa drugs are the most effective means for the symptomatic treatment of Parkinson's disease (PD). With a long course of PD during therapy with levodopa drugs, the clinical picture of the disease changes (clinical pathomorphosis occurs), levodopa-induced dyskinesias and motor fluctuations occur [1]. Already 2 years after the start of taking dopa-containing drugs, the above complications occur in 50% of patients, and after 10 years - in 80–100%, they become an independent maladaptive factor affecting the daily activity of patients [2]. Levodopa-induced dyskinesias most often manifest in the lower extremities on the side of the

body in which the symptoms of PD initially arose and in which the most pronounced manifestations of hypokinesia and rigidity are subsequently noted [3]. Dyskinesia significantly reduces the quality of life of patients, sharply limits their ability to work, and reduces their initiative; patients are forced to change their usual lifestyle. In many patients with PD, due to constant excessive motor activity, body weight decreases, disorders of the cardiovascular system may develop, and generalized hyperhidrosis occurs. In some cases, patients with switch-off dystonias develop a chronic pain syndrome, which may result in the development of affective disorders [4]. Levodopa-induced dyskinesias in patients with PD manifest themselves much earlier at an earlier onset of the disease and intensify as it progresses [5, 6]. According to the results of various studies, the prevalence of levodopa-induced dyskinesia ranges from 64.5 to 85.0% in the general cohort of patients with PD [6]. After starting treatment with levodopa, approximately 10% of patients annually develop motor disorders in the form of fluctuations and dyskinesias [7]. There is a clear connection between the increase in the number of PD patients with dyskinesias and the duration of PD: 1 year of illness - 7-10%, 2-3 years - 30–45%, 5 years – up to 50%, more than 9 years – 57–90% [8]. The severity of the disease at the beginning of levodopa therapy is a more significant risk factor for the development of dyskinesias than long-term levodopa therapy itself [9]. It was found that higher doses of levodopa are more likely to cause dyskinesia [6]. It has been noted that the incidence of dyskinesias is significantly higher in patients with a more pronounced positive response to therapy with levodopa drugs compared to patients with a moderate positive effect.

Materials and Methods

The material for the analysis was the data of patients of the Neurosurgery Department of the Multidisciplinary Clinic of Samarkand State Medical University over the past 5 years and literature data.When choosing treatment methods, it is first necessary to determine the type of dyskinesia, its clinical pattern, and its relationship with taking a single dose of levodopa. The next step should be a review and modification of antiparkinsonian therapy: changing the dose, frequency of administration, replacing short-acting levodopa drugs with long-acting forms, prescribing antidyskinetic drugs (amantadine, clozapine), assessing the indications for functional stereotactic surgery. For peak dose dyskinesia, it is recommended: – replacement of fast-acting forms of levodopa to long-acting forms; – withdrawal of monoamine oxidase (MAO) type B inhibitors, catechol-O-methyltransferase (COMT) inhibitors; – reduction of a single dose of levodopa; – reduction of the dose of levodopa and/or increase in the dose of ADR; – neurosurgical treatment. For dyskinesia (dystonia) after the end of the dose effect, the following approaches to correction are recommended: - prescribing combination therapy (levodopa drugs and long-acting ADRs); - increasing the frequency and/or dose of levodopa drugs; - prescribing long-acting levodopa drugs; - prescribing COMT inhibitors; - adding an MAO type B inhibitor; neurosurgical treatment; - administration of botulinum toxin for local dystonias. For biphasic dyskinesias, it is proposed to use the following methods: - replacement of long-acting levodopa with fast-acting levodopa; - increasing the dose of ADR; - reviewing the prescription of a COMT inhibitor; - modifying the dose and frequency of levodopa; - neurosurgical method; – subcutaneous injections of apomorphine; – duodenal administration of levodopa. To date, sufficient experience has been accumulated indicating the effectiveness of amantadines in the correction of levodopa-induced dyskinesias in PD. The mechanism of action of amantadines in PD is associated with an increase in dopamine synthesis in presynaptic terminals, an increase in its release into the synaptic cleft

with inhibition of dopamine reuptake, stimulation of dopamine receptors, as well as with the anticholinergic properties of the drugs [24]. In addition, amantadines are antagonists of NMDA receptors, and therefore they are assumed to have neuroprotective and antidyskinetic effects [25]. Amantadines are in most cases effective in reducing the severity of dyskinesias caused by taking levodopa. This effect may decrease several months after administration, but in some patients it may persist for a longer time [26]. At advanced stages of PD, as a result of increasing dopamine deficiency, the sensitivity of glutamate receptors in the striatum increases. Impaired functioning of the pallidothalamocortical motor pathway also plays a certain role in the occurrence of dyskinesias [14]. The importance of genetic factors (polymorphism of D 2 receptors) is also considered [27, 28]. The negative effect of nigrostriatal dopamine deficiency on the glutamatergic system is associated with the disappearance of physiological blockade of striatal glutamate receptors.Amantadines prevent glutamatergic hyperactivity and reduce the manifestations of dyskinesias. In a double-blind crossover study, 60% of patients receiving amantadine for 3 weeks experienced a decrease in dyskinesias without worsening the antiparkinsonian effect of levodopa [26]. Another randomized, double-blind, controlled trial noted a 45% reduction in the severity of levodopa-induced dyskinesias when treating amantadine patients with late stages of PD [25]. In a double-blind, placebo-controlled, randomized study, patients were prescribed amantadine sulfate at a dose of 100 mg for 3 weeks. There was a decrease in the severity of dyskinesia (by 24%) and a decrease in the duration of the off period with dyskinesias [29]. In a randomized, double-blind crossover study, the effect of an injectable form of amantadine sulfate on dyskinesias was studied. 2 hours after the start of administration of amantadine sulfate (200 mg in 500 ml solution), there was a decrease in the manifestations of dyskinesia by 25–32% on the AIMS scale and self-assessment diaries in comparison with the placebo group [30]. In some patients, dyskinesias due to DBS STN are reduced when one of the superior electrodes is located in the hypothalamic region near the Forel field, where the ansa lenticularis and the fasciculus lenticularis pass by the GPi and enter the thalamus [38]. According to the literature, bilateral NS STN causes significant reductions in dyskinesias (60 to 80%) and motor fluctuations (46 to 51%) in most patients [39–48]bilateral NS STN causes a significant reduction in dyskinesias (from 60 to 80%) and motor fluctuations (from 46 to 51%) in most patients [39–48]bilateral NS STN causes a significant reduction in dyskinesias (from 60 to 80%) and motor fluctuations (from 46 to 51%) in most patients [39–48]

Thus, the severity of dyskinesias against the background of NS subcortical structures corresponded to “very mild” (no more than 25% of waking time) or “mild” (26–50% of waking time) indicators versus moderate indicators of initial testing before surgery. The daily equivalent dose of levodopa decreased by 58% by the 6th month of the postoperative period and remained virtually unchanged by the end of the 1st year of observation.

Conclusion

The pathogenesis of levodopa-induced dyskinesias in PD remains poorly understood. Data from new studies concerning degeneration of the nigrostriatal dopamine system indicate the likely involvement of the basal ganglia glutamatergic system in the pathogenesis. The antidyskinetic effect of amantadine is associated with blockade of central NMDA receptors. Amantadine prevents glutamatergic hyperactivity and reduces the manifestations of dyskinesias, which significantly worsen motor, daily activity and quality of life of patients. Based on the results of the study, it can

be argued that amantadine sulfate (PC-Merz) has an antidyskinetic effect and can be recommended for the correction of various types of levodopa-induced dyskinesias in patients with PD. Chronic NS of the subcortical structures of the brain leads to a significant regression of drug dyskinesia peak dose, probably due to the possibility a significant reduction in daily doses of dopaminergic drugs and, apparently, due to the direct influence of the NS on the functional state of the extrapyramidal system. The algorithm for choosing a method for correcting dyskinesias should be determined primarily by changes in pharmacotherapy (doses, combinations of drugs), including the addition of the NMDA receptor antagonist amantadine. If pharmacotherapeutic drugs are ineffective approaches in case of severe drug-resistant dyskinesias, neurosurgical treatment is recommended. Currently, numerous studies are being conducted on the effectiveness of new NMDA receptor antagonists, adrenergic receptor antagonists, adenosine receptor antagonists, nicotinic receptor agonists, partial dopamine agonists, new MAO type B inhibitors, serotonin receptor agonists, anticonvulsants [59]; The study of the effect of chronic stimulation of various brain targets for the correction of dyskinesias in PD at advanced stages continues.

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