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Use of the New Levodopa Agent Stalevo (levodopa/carbidopa/entacapone) in the Treatment of Parkinson's Disease in Out-Patient Clinical Practice (the START-M open trial)

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Despite the significant symptomatic effects of levodopa, stable 24-h treatment responses are in the vast majority of patients replaced 2–3 years from the start of treatment by oscillations in motor symptoms (fluctuation, dyskinesia), amelioration of which requires addition of constant (physiological) stimulation of postsynaptic dopamine receptors. To some extent this is provided by Stalevo, which contains levodopa and two enzyme inhibitors: the DDC inhibitor carbidopa and the COMT inhibitor entacapone. The results obtained in the present study demonstrated the advantages of Stalevo over traditional agents in patients with the "wearing off" and "on-off" phenomena.

KEY WORDS: Parkinson's disease, fluctuation, "wearing off" phenomenon, constant dopaminergic stimulation, COMT, entacapone, Stalevo.

Parkinson's disease (PD) is known to result from degeneration of dopaminergic neurons in the substantia nigra, with decreases in dopamine levels in the basal ganglia, leading to characteristic motor disorders in the form of bradykinesia, rigidity, and tremor [4]. The sequelae due to disease progression and increasing dysfunction of non-dopaminergic systems consist of postural instability, along with mental and autonomic disturbances.

The "gold standard" in the treatment of PD since the end of the 1960s has consisted of levodopa preparations, which have the ability to provide long-term support of motor activity, to preserve the ability to work and the quality of life, and to decrease lethality. Despite its significant effects, levodopa treatment in the vast majority of patients shows oscillations in the severity of motor impairments from 2–3 years from the onset of treatment, and this affects quality of life. Motor fluctuations (the "wearing off" phenomenon, whereby single doses lose their effect, the "on-off" phenomenon, freezing) develop, along with various therapeutic dyskinesias (peak-dose choreiform dyskinesia, end-dose dystonia, biphasic dyskinesia, etc.) [1, 6, 7, 10, 19].

The leading pathogenetic factor in the development of motor fluctuations and dyskinesias is the non-uniform (pulsatile) stimulation of postsynaptic neurons in the striatum. On the background of progressive death of dopaminergic neurons in the substantia nigra, levodopa is converted to an ever greater extent to dopamine in neighboring glial cells and non-dopaminergic neurons, which lack a mechanism for storing and controlling the secretion of this transmitter.

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After taking the next levodopa dose, dopamine is therefore released into the intercellular space. As a result, stimulation of dopamine (DA) receptors comes to depend on oscillations in the blood levodopa level and ceases to be tonic, as in physiological conditions, but becomes pulsatile, which in turn changes the functional state of postsynaptic striate receptors [5–7, 19].

Thus, amelioration of the major motor complications of prolonged levodopa treatment requires achievement of a constant (physiological) stimulation of postsynaptic DA receptors, which can be obtained in two ways: 1) by stabilizing the dopamine level by increasing the frequency of taking levodopa or its dose, using long-acting formulations, by constant intravenous or enteral infusions of levodopa, by addition of catechol-O-methyltransferase (COMT) inhibitors or monoamine oxidase (MAO) B inhibitors; 2) by direct stimulation of DA receptors using DA receptor agonists [7, 8, 14, 15, 18].

Most levodopa in the body is known to be metabolized by DOPA-decarboxylase (DDC), the remaining 10% of the active substance being methylated by COMT. Addition of a DDC inhibitor (carbidopa or benserazide) to levodopa increases the peak plasma levodopa concentration and increases its $T_{1/2}$ to 90 min. However, use of a two-component levodopa preparation (levodopa/DDC inhibitor) results in sharp increases in the activity of the alternative pathway of levodopa catabolism – methylation (COMT). Since the end of the 1990s, one approach to substituting for the deficiency of dopamine has been to add COMT inhibitors to two-component levodopa preparations. The safest and most widely used member of this group of therapeutic agents is entacapone [5, 6, 22].

Addition of entacapone to levodopa/DDC inhibitor combinations increases the bioavailability of levodopa by 35–50%, extends the blood levodopa halflife by 85% (from 1–1.5 to 2.5–3 h), and gives a more stable blood levodopa concentration [8, 14, 20]. A number of multicenter double-blind, placebo-controlled trials have tested the effects of entacapone mainly in patients with motor fluctuations. Prolongation of the actions of single doses of levodopa (by about 40 min) have been demonstrated, along with increases in the duration of on periods by 0.5–2 h/day and decreases in the duration of off periods by 0.9–1.3 h/day [5, 9, 11, 20, 22].

In 2003, the new combined levodopa preparation Stalevo, containing both a DDC inhibitor (carbidopa) and a COMT inhibitor (entacapone) was introduced into international clinical practice. Open studies performed in a variety of therapeutic institutions and following a single protocol [1–3] have been of great significance for assessing the place of this agent in daily neurological practice.

An open study of Stalevo for the treatment of patients with motor fluctuations in PD was undertaken at six regional out-patient neurology clinics in Moscow with the aim of evaluating the efficacy and tolerance of this agent.

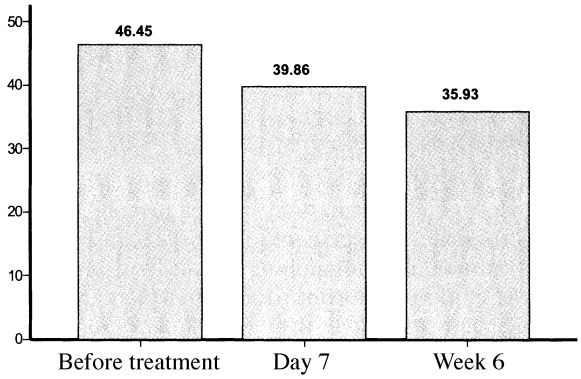

Fig. 1. Changes in UPDRS points scores (ordinate) during treatment with Stalevo on day 7 and at the end of week 6 of the trial. Differences between all measures were statistically significant at $p < 0.001$.

MATERIALS AND METHODS

The study included 50 patients (28 women, 22 male) with a mean age of 66.7 ± 5.8 years.

All patients had idiopathic PD with motor fluctuations (wearing off of the effects of single levodopa doses, on-off phenomenon) and were under treatment with two-component levodopa agents at doses of up to 750 mg/day. The duration of illness averaged 6.8 ± 3.1 years and the duration of levodopa treatment averaged 59.5 ± 27.6 months. Patients took a mean daily dose of levodopa of 540 ± 119 mg. Bilateral parkinsonism without balance disorder (Hoehn and Yahr stage 2) was seen in 37.9% of patients; 41.4% had stage 2.5 disease, in which mild bilateral motor impairments were combined with retropulsion which could be overcome; 32% of patients had stage 3 PD with postural instability and intermittent need for assistance. Motor fluctuations in the form of wearing off of the daily levodopa dose were present in 61% of patients, predictable on-off switching was seen in the remaining 39% of patients, and dyskinesia was present in 27.6% of patients.

The Stalevo dose was determined in accord with the daily levodopa dose which the patients were taking prior to the trial. Treatment used Stalevo from Orion.

Patients were investigated three times during the trial. The first screening investigation was performed before starting Stalevo and follow-up attendances took place at the end of the first and sixth weeks of treatment. Investigations included clinical and neurological examination, with quantitative assessment of motor derangement using the unified PD rating scale (UPDRS). The severity of motor fluctuations was evaluated using a questionnaire assessment of variations in motor function and a self-assessment diary of the patients' state. A questionnaire assessing the overall clinical impressions of the patient and physician was completed at the end of the treatment period.

TABLE 1. Changes in UPDRS Subscale Scores during Treatment with Stalevo, points

Subscales	Before treatment	Treatment week 6
Mental functions	3.6 ± 1.9	2.5 ± 1.7*
Activities of daily living	14.3 ± 5.1	10.7 ± 5.1*
Motor impairments	24.2 ± 8.3	19.4 ± 9.9*
Complications of treatment	4 ± 2.6	3.3 ± 2.2**

Note. Differences were statistically significant at: *$p < 0.0001$; **$p < 0.001$.

TABLE 2. Assessment of Changes in Patients' State during Stalevo Treatment

Change in state	Patient assessment, %	Physician assessment, %
No change	7	3.5
Insignificant improvement	41.3	24.1
Significant improvement	51.7	72.4

RESULTS

By week 6 of the trial, positive dynamics were seen on the background of Stalevo treatment, with a 29.2% reduction in the UPDRS score (see Fig. 1).

There were improvements not only in the total points score, but also in separate UPDRS subscales: by 6 weeks of Stalevo treatment, there were significant reductions in behavioral impairments and mood (by 30.5%), with a 25.1% improvement in the activities of daily living (speech, gait, dressing, turning over in bed), a 24.7% decrease in hypobradykinesia in the limbs and axial musculature, rigidity, and tremor (see Table 1).

During Stalevo treatment there were no increases in the therapeutic dyskinesia seen previously in some of the patients. On the contrary, Stalevo treatment was associated with significant reductions in the severity of motor fluctuations, 86% of the patients reporting decreases in the duration of off periods (by an average of 1.7 ± 1.3 h per day: from 5.8 h before treatment to 4.1 h after treatment) and a 33% reduction in the number of off periods (motor variation questionnaire data), from 5.138 to 3.862 units.

Among side effects, fewer than 10% of patients reported nausea, orthostatic reactions, and headache, none of which required corrective treatment.

Differences between the patients' and physicians' overall impressions of the action of the agent should be noted: patients more often indicated insignificant improvements in their condition, while physicians more frequently noted improvements as significant. Physicians' assessments showed a better correlation with changes on the UPDRS. These data are presented in more detail in Table 2.

DISCUSSION

This trial demonstrated the high efficacy and good tolerance of Stalevo in patients with motor fluctuations. As compared with the traditional agent levodopa (levodopa + DDC inhibitor), Stalevo (levodopa + DDC inhibitor + COMT inhibitor) provided better control of symptoms during the day, improved daily and motor activity during "on" periods, decreased the duration of "off" periods, and improved the quality of motor activity during these periods. Thus, it became possible to optimize the positive clinical effects in patients previously treated with two-component levodopa formulations and to improve treatment tolerance by transferring these patients to the three-component levodopa preparation Stalevo.

Previous clinical trials have shown the value of the earliest possible prescription of entacapone to patients on appearance of the first signs of wearing off of the effects of levodopa doses, as it provides good control of symptoms throughout the day, leads to improvements in measures of motor activity during the day, and allows reductions in the daily levodopa dose [11, 12, 20, 22]. Prescription of entacapone with standard levodopa formulations in patients without motor fluctuations produced insignificant improvements in motor function on the movement scales of the UPDRS but significantly improved quality of life [12, 16]. In cases in which treatment was started immediately with the combination of levodopa + DDC inhibitor + entacapone, better control of parkinsonism symptoms on the third part of the UPDRS was seen with lower daily levodopa doses for at least five years, as compared with patients in whom entacapone was added to the treatment

schedule six months after the initiation of levodopa treatment [21].

Studies describing the effects of early prescription of entacapone on various motor fluctuations and dyskinesias are now appearing. Thus, a number of trials [17, 22] have shown that simultaneous treatment with levodopa, a DDC inhibitor, and a COMT inhibitor (entacapone) provided stable plasma levodopa levels, this providing tonic stimulation of dopamine receptors in the striatum, which decreases the risk of developing motor complications. Treatment of patients with MPTP-induced toxic parkinsonism using Stalevo prevented the development of therapeutic dyskinesias [13]. The ongoing multicenter clinical trial STRIDE-E aims to provide evidence in primates. If the results are positive, the recommendation will be to start levodopa treatment with Stalevo as an agent providing not only effective control of disease symptoms, but also significant improvements in the prospects of patients with PD.

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