Viusid/Alzer efficacy in the treatment of Parkinson's disease associated fatigue

José Luis Giroud Benítez[1], María del Rosario Abreu Vázquez[2], Ovidio Gustavo Rodríguez Miranda[3], Marisol Torres Monteagudo[4], María Elena Tacoronte Morales[4], Guillermo Toledo Sotomayor[4], Yoandra García Sánchez[4], Enerys Mendoza Tirado[4], Víctor Frades García[4], Félix Mariano Guevara Ferrer[4], Jorge Luis Mato Oliva[4], Estela Amarante Justiniani[4], Fernando Martín Ordoño[4], Milene Vázquez Martínez[4] and Mayra Carrasco García[3]

Abstract

INTRODUCTION Fatigue is a very frequent symptom among patients with Parkinson's disease (PD) for which there is no effective treatment. In clinical studies of patients with viral and liver diseases, fatigue improvement has been demonstrated with the used of Viusid and Alzer. METHODS. A randomized, double blind and placebo controlled clinical trial was carried out in 100 patients, 50 in each group, from October 2009 to May 2011. Group A or the study group, received combined Viusid and Alzer treatment and group B or the control group, placebo. RESULTS. At 3 months in the study group only 2 showed fatigue (4%), which was maintained at six months and one year, with significant differences when compared to the control group. There was also improvement in fatigue severity, evaluated by PFS. CONCLUSIONS. The combined use of Viusid/Alzer nutritional supplements is effective in PD patient treatment, therefore it should be evaluated in studies with larger number of patients and a methodology that supports this indication.

Key words

Parkinson's disease, fatigue, Viusid, Alzer, nonmotor symptoms

INTRODUCTION

Parkinson's disease (PD) is frequent, mainly affecting persons older than 60 years, increasing its frequency with age showing a peak at 80 years (1-3). This is a degenerative disease that has a chronic and progressive clinical course. Its treatment is directed towards motor symptoms and nonmotor ones, such as depression, psychosis and dementia, but there is no effective treatment against fatigue, which affects approximately 50% of the patients (4).

Scientific evidences published on Viusid treatment of chronic hepatopathies (5), and febrile syndrome (6), have demonstrated positive effect on fatigue in these patients and that Alzer, composed by gingko biloba and carnitine, improves muscular function (7), and thus fatigue in healthy subjects and multiple sclerosis patients (8,9).

Therefore, due to lack of specific treatment for this frequent clinical condition, it was decided to carry out a clinical trial to demonstrate efficacy of the nutritional supplements Viusid and Alzer against PD associated fatigue.

[1]Corresponding author: José Luis Giroud MD, Neurologist, PhD, Assistant Professor, Dr. Salvador Allende Hospital, Calzada del Cerro St. No. 1551, Havana, Cuba. email: jlgiroudbenitez@yahoo.com

[2]Biostatistician, Gastroenterology Institute, 25th St. No. 503 between H and I, Vedado, Havana, Cuba

[3]MD, General Practitioner, Dr. Salvador Allende Hospital

[4]MD, Neurologist, Dr. Salvador Allende Hospital

Methods

A clinical trial was carried out to determine the effect of the nutritional supplements Viusid and Alzer in the treatment of PD associated fatigue. This study was carried out from October 2009 to May 2011 and PD patients were included according to the London Brain Bank criteria (10).

PATIENTS

Our study group was formed by consecutive patients with PD diagnosis that came to the Dr. Salvador Allende Clinical Surgical Hospital because of motor disorders during the time established. All the patients from 40 to 90 years of age that gave their signed consent were included. Criteria used were bradykinesia and at least one of the cardinal signs: tremor at rest and rigidity of asymmetric and insidious onset and unequivocal response to Levodopa, given by at least 50% improvement in the motor UPDRS (Unified Parkinson Disease Rating Scale) after receiving Levodopa with an inhibitor of peripheral decarboxilase (Benserazide or Carbidopa) at a dose lower or equal to 1 gram, for at least one month, without presence of atypical signs (10).

ETHICAL PROCEDURES

To warrant compliance with this research, and to enhance the safety of patients participating in this study, the inconveniences, predictable risks, as well as the welfare of the study subjects were taken into account. All patients were given enough supplementary information about the product to be used. All patients were given an informed consent form, to be read and signed if they agreed with the investigation. This form was kept as an annexed document. They all agreed with the criteria of the study. All patients were continuously evaluated by the medical researchers in charge of the study, receiving medical attention whenever necessary. The standards established in the Declaration of Helsinki were complied with and the study was approved by the Ethics Committee of the Salvador Allende Clinical Surgical Hospital. This research was registered in ClinicalTrials.gov (NCT01016470).

DESIGN OF THE STUDY

Randomized, double blind and placebo controlled clinical trial. The minimum sample size was 100 patients, 50 in each group. In group A or the study group, combined therapy with Viusid and Alzer (Catalysis S.A.) was used. In group B, the control group, a placebo, prepared at the Catalysis S.A. laboratories was administered with the same frequency and dose as in group A. Each patient was assigned a treatment schedule according to the random list prepared by the Department of Biostatistics of the Catalysis Laboratory. A group of sealed envelopes, one for each patient was kept in the institution. They were consecutively numbered and contained the corresponding treatment schedule.

Viusid is a nutritional supplement in sachets, with the following ingredients: malic acid (0.666g), glucosamine (0.080g), arginine (0.666g), glycine (0.333g), glycyrrhizinic acid (0.333g), ascorbic acid (0.020g), zinc sulfate (0.005g), calcium panthotenate (0.002g), pyridoxal (0.0006g), folic acid (0.0070g), cyanocobalamin (0.0003mg), sodium methylparaben (0.003g), neohesperidine (0.005g), lemon (0.666g), mint (0.033g), honey (0.833g), and guar gum (0.650g).

Alzer comes as capsules and contains 20.5 mg carnitine, 20.5 mg lipoic acid, 40.0 mg ginkgo biloba, 214.5 mg dry lettuce extract and 207.0 mg guar gum. Oral administration was used for both groups (A and B), with a frequency of three times a day, taken with foods and separate from regular PD medication.

Criteria for treatment interruption were: presence of severe adverse events with life risk (grade III adverse events, WHO classification), voluntary withdrawal, appearance of an associated disease masking the expected results, treatment interruption and patient's death.

The list was automatically prepared and kept at the Department of Biostatistics and Research of the Catalysis Laboratory, considered the contact in case of need to decode any patient throughout the study. Assignation of the patients was blinded for the researchers, after the patient met inclusion criteria and signed the consent to participate in the study. A simple randomization method was used. The code was revealed to the researchers once the study had concluded.

The main evaluation criterion was the Parkinson fatigue scale (PFS), applied at onset (day 0), three months, six months and one year. This scale has 16 items, with scores from 1 to 5 according to the patient's criterion. Final evaluation can be done in two ways, using the total scale punctuation, with a 32 cutoff point, or by the mean of the evaluations with a cutoff point of 4, the one used in the study. These evaluations were always carried out by the same researcher, who did not know the group to which a patient belonged. Secondary criteria were the presence of fatigue, the motor state by total Unified Parkinson's Disease Rating Scale (UPDRS) and subscales, depression level using the Hamilton scale and cognitive impairment by Mini-Mental State Examination (MMSE), which were measured at each evaluation. Control variables were sex, age, disease duration and laterality of motor impairment. Difference between initial and final score was evaluated and considered a sign of evolution in the different groups.

Information was collected in the work books prepared for this study. This information was gathered in a database, using the SPSS version 18.00 system.

STATISTICAL ANALYSIS

Exploratory analysis of the data was carried out using the mean, standard deviation and median for the quantitative variables. Qualitative variables were summarized using absolute and relative frequencies. To analyze group differences, the Chi square test was used for categorical variables and the Wilcoxon-Mann-Whitney test for quantitative variables. Result analysis included all patients who received at least one administration of the product (intention to treat analysis). For the variables: PFS (main evaluation criterion), UPDRS, Hamilton and MMSE scores, the Wilcoxon signed-rank test was used to evaluate changes before and after the intervention and the Wilcoxon-Mann-Whitney test for group differences. Safety evaluation was carried out on all patients that had at least one evaluation after treatment onset.

Twenty five percent of improvement was estimated in the PFS of the study group. The study was designed for 80% potency to detect an absolute difference of 35% improvement in PFS: 25% in the study group and 10% in the control. Considering a type I error of 5%, 100 patients were finally in-

cluded, 50 in each group. A significance level of 5% was assumed for all confidence intervals and statistical significance tests; all hypotheses had bilateral formulation.

Results

During the study, 119 patients with Parkinson's disease diagnosis and the possibility of being chosen were evaluated; 7 of them refused to participate in the clinical study and 12 did not fulfill the established criteria as shown in figure 1. Of 100 randomized patients, 50 received Viusid/Alzer and 50, placebo. In the study group, a patient was lost during follow up and three, in the control group, thus 96 patients completed the study.

Baseline patient characteristics are shown in table 1, where parity between groups is observed, except for the duration of the disease and the score obtained in the total UPDRS scale.

At the beginning of the study, approximately 48% of the patients showed fatigue symptoms according to the PFS scale with an equal distribution in the study group: 25 with fatigue and 25 without it, and in the control group: 23 with fatigue and 27 without it. At 3 months, 18 patients in the control group had fatigue and 22 at 6 months and 12 months. In the study group, only 2 patients showed fatigue at 3 months, 4%, which was the same at 6 months and one year, as can be observed in the following graphic.

Mean PFS in both groups is represented in table 2, where a highly significant difference can be observed from the third month of evaluation, maintained until the end of the study.

There were no significant differences between presence or severity of fatigue and the different clinical variables measured in the patients of our study.

Regarding adverse events, three patients showed transient epigastralgia; two patients, early insomnia and one patient, headache. In none of the cases did the treatment have to be modified and they continued in the study until its end.

It is possible to observe PFS improvement after the first evaluation, which is maintained throughout the whole study.

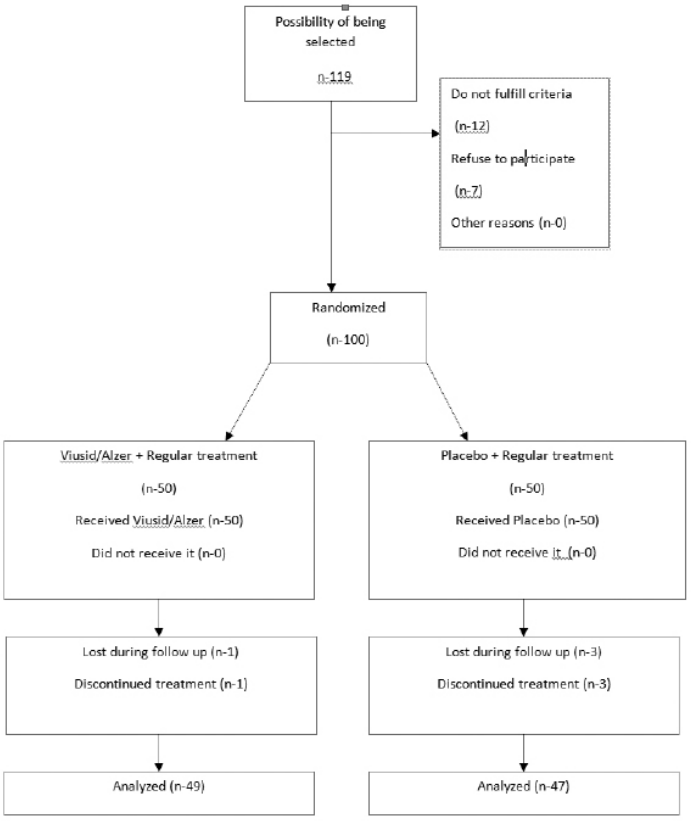


Figure 1. Patient flow chart during the study

Table 1. Baseline characteristics of the patients evaluated at study onset

Variables	Viusid group (49)	Placebo group (47)	p value
Age, in years (mean/SD)	62.58 / 10.8	62.34 / 8.6	p=0.90
Duration of the disease, in years (mean/SD)	4.6 / 2.9	2.6 / 1.8	p=0.01*
Sex (Male/Female)	31 / 19	32 / 18	p=0.83
FPS (mean/SD)	40.9 / 12.6	38.2 / 13.4	p=0.93
Presence of fatigue (yes/no)	25 / 25	23/27	p=0,69
UPDRS motor (mean/SD)	35 / 19.0	31.7 / 16.2	p=0.08
MMSE (mean/SD)	26.9 / 2.6	27 / 2.3	p=0.11
Hamilton (mean/SD)	6.8 / 6.2	5.3 / 4.5	p=0.30

*Significant difference

Table 1. Baseline characteristics of the patients evaluated at study onset

Discussion

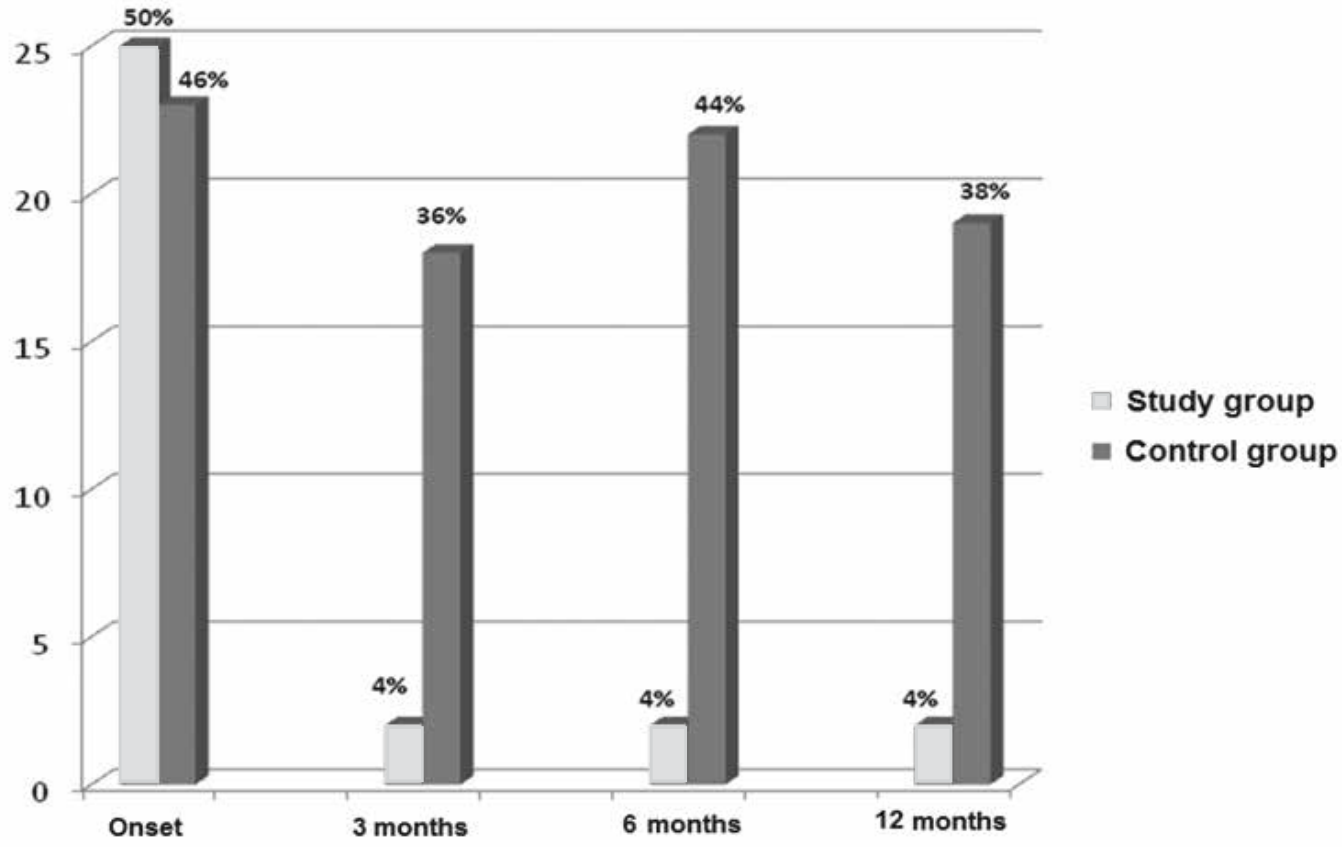
Differences observed in the baseline characteristics of the patients regarding disease duration and total UPDRS score are due to patients being included at different times of their disease evolution. In spite of this, there was no repercussion on the results of the study, since there was no relation between fatigue as the main variable and the remaining variables evaluated.

Improvement of fatigue was observed both in frequency and severity in the study group. Fifty percent of the patients using Viusid/Alzer showed fatigue at onset, whereas only two had this symptom in the remaining evaluations (2 %). Also, when evaluating intensity there was noticeable improvement in the study group, so we consider that considering the effectiveness of these nutritional supplements observed in this study and the few adverse events, this may be a commendable fatigue treatment option for PD.

Since the discovery of dopamine deficiency as cause of the motor symptoms, PD treatment has been aimed in that direction, and nonmotor symptoms have been underrated for a long time. However, in the last decades publications indicating their frequency and repercussion in the patient's quality of life and treatment possibilities have increased.

Among nonmotor symptoms, one of the most frequent is fatigue, which is conceptually a complex symptom and occasionally, hard to explain. In PD patients it can be confused with depression or motor symptoms that characterize this disease. The first descriptions showed small percentages, but in the last years, with the development of clinical instruments that allow more exact determination, they are over 40% in many studies. In the PRIAMO study (4), almost 100% of the patients showed nonmotor symptoms, but the most frequent one was fatigue in 58.1%. In our sample, 48% of the patients had fatigue with a PFS cutoff point equal or higher than 4, similar to different studies published in this regard.

Patients in our study showed a statistically significant improvement at 3 months of the first or initial evaluation. The



	Study group		Control group		p value
	mean	SD	mean	SD	
PFS at onset	3.3	0.88	3.2	0.88	0.57
PFS at 3 months	2.32	0.55	2.96	1	<0.001
PFS at 6 months	2.2	0.49	3.14	0.84	<0.001
PFS at 12 months	2.2	0.53	3.08	0.88	<0.001

Table 2. Distribution of the mean PFS, during the four evaluation periods and its statistical significance

design of this study did not include an evaluation earlier than 3 months, but many patients referred that a few days after treatment onset they already felt improvement of the fatigue. Data obtained showed differences in two ways: as reduction of fatigue, cutoff point 4 according to PFS, which in the study group was initially detected in 50% of the patients with fatigue and after the third month in only 4%, value maintained throughout the rest of the evaluations. It is not known whether this fatigue improvement continued after suspension of the nutritional supplements. Severity of the fatigue observed was noticeably reduced due to the reduction in the PFS mean, showing high statistical significance from the first evaluation at 3 months. This fatigue improvement had not been observed in any of the clinical trials published. Reports of pramipexole use (11), showed that only patients with less disease severity (Hoehn and Yahr, stages I and II) improved, and the study using methylphenidate (12) or modafinil (13,14), did not show sufficient evidence of being efficient and safe in the treatment of PD fatigue. Thus, the combined use of Viusid/Alzer, can be considered in this sense.

There is no definition, specific treatment, or golden standard to evaluate fatigue, thus we are far from the last word in this respect. The reason why PD patients suffer fatigue is not fully known. In many studies there is no correlation between disease severity, duration, clinical type, Parkinson medication dose and the type of drug used. Some authors have found elevated frequency of fatigue in patients with PD and depression, but also in non depressed ones (15).

We consider fatigue improvement observed in this study not directly related to PD and the possible causes that justify this symptom are: serotoninergic reduction at the level of the basal ganglia or insular dopaminergic reduction.

The evidence we have is that Viusid improves the well-being of healthy people, patients with hepatopathies (5) and patients with acute viral diseases (6). This is a nutritional supplement providing amino acids, zinc, calcium and antioxidant substances, which could explain this effect. Arginine is one of Viusid components, a precursor of growth hormone, which is reduced in elderly people, with a yearly reduction rate of 1.4%, after 35 years of age. That is, at the most frequent PD presentation age there is a considerable reduction of this hormone. This hormone has anabolic effect and its reduction may be the cause of muscle fatigue and fibromyalgia (17).

The action on the oxidative stress (OS) seems to us the main factor in fatigue improvement associated to the use of Viusid and Alzer nutritional supplements. It is known that at muscular level OS can cause fatigue (18-20) and these supplements act as antioxidants through the action of several com-

ponents such as: neohesperidine and ascorbic acid. There is also improvement of the OS due to B complex and folic acid, which theoretically decrease homocysteine levels in blood. This amino acid induces oxidative stress and damage at the endothelial vascular level, causing a reduction of tissue perfusion and atherogenesis (21-23). It has also been reported that in PD patients high levels of homocysteine are associated to the levodopa treatment (24), so these elements would further support the use of nutritional supplements in these types of patients (25).

Another element is zinc, which functionally stabilizes the immune system, oxidative stress and muscle fatigue. Zinc is necessary for muscle function; its decrease at plasma level has been observed in persons with fatigue. Although reduction of Zn levels in PD patients has not been demonstrated, it could contribute to improvement, associated to Zn use in these patients (26,27). Calcium is essential for muscle function; decrease of its release in the endoplasmic reticulum and reduction of its storage have also been observed in patients with fatigue. Supplements containing calcium favor muscle contraction and improve fatigue (28,29).

Arginine increases muscle capacity in preclinical studies in rats and reduces the oxidative stress induced by hypoxia and muscle fatigue. In physically untrained individuals, fatigue may improve, for example in patients with Parkinson's disease (310).

Studies have demonstrated that reduced levels of serotonin at the basal ganglia and limbic system, as well as dopamine decrease at the insula, are related to the presence of fatigue in PD patients (31). Since we have no evidence that nutritional supplements act at this level, the improvement observed in this study is not exclusive of PD patients.

With these results we may conclude that the use of the combined nutritional supplements Viusid/Alzer is effective for fatigue treatment in PD patients, thus it should be evaluated in studies with larger number of patients, for longer time and maybe in other diseases to demonstrate safety and efficacy of these supplements in fatigue.

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