

ARTÍCULOS ORIGINALES

Protein intake and the use of levodopa in patients with Parkinson's disease

Ingesta de proteínas y el uso de la levodopa en pacientes con enfermedad de Parkinson

Bianca de Moraes Fracasso (1)

Maite Barcelos Moraes (1)

Rosane Gomez (2)

Arlete Hilbig (3)

Estela Iraci Rabito (1)

ABSTRACT

Levodopa is the principal pharmacological treatment for Parkinson's disease (PD); however the protein content in diet may compromise its effectiveness. The aim of this study was to investigate the relationship of protein intake and the use of levodopa in ambulatory patients with PD. Thirty four PD patients were assessed for protein intake, evaluating the relation energy-protein intake by means of a register. An intake of 1762 kcal/day, 70.9 g of protein/day equivalent to 16.6% of the total energy intake as protein at a level of 1.1 g/kg bw/day. Of all patients, 47.1% took their medications with meals. We conclude that the studied patients consume more protein in their diet than those recommended for PD, with half the sample taking the medications with meals, which may affect the treatment.

Key words: neurodegenerative diseases; high protein diet; drug-food interactions; carbidopa.

(1) Department of Nutrition, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre RS, Brazil

(2) Department of Pharmacology, Institute of Basic Health Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre RS, Brazil

(3) Department of Clinical Medicine, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre RS, Brazil

Author correspondence:

Bianca de Moraes Fracasso

Department of Nutrition

Universidade Federal de Ciências da Saúde de Porto Alegre
Porto Alegre RS, Brazil

Fone: (51) 93317383 / (51) 82538232

E-mail: biancafracasso@gmail.com

Este trabajo fue recibido el 2 de Octubre de 2012
y aceptado para ser publicado el 10 de Marzo de 2013.

INTRODUCTION

Parkinson's disease (PD) is a disorder caused by degeneration of dopaminergic neurons in the nigrostriatal pathway (1-3), resulting in a decrease of dopamine production in this region (4). The causes of degeneration are not yet fully elucidated. Usually affects people over 50 years, is more prevalent in men and initially presents the following motor symptoms: resting tremor, bradykinesia, muscle rigidity and loss of postural reflexes with shuffling gait (1, 3, 5, 6). Progression of the disease can involve other signs/symptoms such as dementia, memory and speech problems and a motor impairment of tongue, larynx and food retention in pharynx(5). These symptoms may affect food intake of patients with PD and consequently may result in weight loss and malnutrition, impairing the nutritional status of these individuals (1, 7).

The treatment of PD aims to increase dopamine levels and alleviate the symptoms (3). For this purpose, drugs are used such as inhibitors of dopamine degradation, dopaminergic

agonists (8), dopamine reuptake inhibitors and anticholinergic drugs (9), as well as a precursor of dopamine, L-DOPA (levodopa), which is the most frequently drug used in the PD treatment(8,10).

Concomitant use of medications and foods can interfere with the pharmacokinetics and pharmacodynamics of drugs, as well as in digestion, absorption and utilization of nutrients (11). In this condition, the administered drug may not have the required drug effect and food not exercise the nutritional function expected. It happens because in some cases the uptake of a nutrient has the same mechanism and absorption site of drug (11), such as aminoacids and levodopa that compete for the same active transport mechanism in the gastrointestinal tract and the blood-brain barrier (1).

The principles of PD patients nutrition therapy aims to reduce the interaction between levodopa and aminoacids in the diet. Based on this, the aim of this study was to investigate the adequacy of the protein intake recommendation and the levodopa regiment in patients with PD.

SUBJECTS AND METHOD

This was a descriptive study, with a quantitative approach, performed in the Clinic of Movement Disorders and Dementias of Santa Casa Hospital Complex of Porto Alegre, during October 2010 to August 2011. This research and consent term were approved by the Ethics Committee on Human Research of the Federal University of Health Sciences of Porto Alegre (10/681).

The sample included patients of both sexes, with a clinical diagnosis for Parkinson's disease. Patients with other parkinsonism form, which were not treat with drugs to PD, no physical condition to perform anthropometric measurements and without cognitive capacity or no care a provider who could report drug/nutrient interactions, were excluded.

Participants were submitted to nutritional assessment with implementation of Mini Nutritional Assessment (MNA) (12), which includes anthropometric measurements of: weight, measured with scales calibrated platform Welmy® with subdivision between 100 g and maximum 150 Kg; height, estimated by measuring the half-span (HS), due to most patients had postural changes; estimate of body mass index (BMI) by Lipschitz(13), mid-arm circumference (AC) (14) and calf circumference (CC)(14), measured with anthropometric tape. Dietary intake assessment, life condition, health perception and nutritional status were evaluated in patients. Furthermore, they were asked to fill the estimated consumption record (ECR) of food(15) and medications for three days. To assist the ECR filling, in the evaluation day a verbal and visual training was conducted with photographic material support about household sizes and food portions. A copy of this material was given to the participants. After the completed registration, the food intake was calculated using food composition tables and household sizes(16, 17) using Excel® software. It was done a list of the medications used with the number of drugs administered, the administration schedules and the proximity to meals.

Data were organized into a database and analyzed using absolute and relative frequency. The results of consumer records were described as mean ± standard deviation. Data normality of intake and anthropometry evaluation was analyzed using the Kolmogorov-Smirnov test (KS).

RESULTS

This study included 34 patients, 20 men (58.8%) and 14 women (41.2%). Table 1 presents the profile of the studied

population. No patients were classified as under nutrition according to BMI, while 53% presented risk of malnutrition, according to MNA.

In the evaluation of dietary intake (Table 2), the protein intake was higher in the daytime compared to nighttime. That is, between breakfast and afternoon snack, 70.4% (49.5 g) of total daily protein was consumed, and in this period men consumed 70.6% (54.2 g) and women, 70.0% (42,9 g).

The average amount of different drugs taken per day was 3.9 ± 2.2. The men used 4.0 ± 2.5 of different medications while women consumed 3.8 ± 1.9. In this study, a total of six different types of PD treatment medicaments were recorded. All patients received levodopa associated with a peripheral dopa decarboxylase inhibitor (carbidopa or benserazide).

About the time of drugs consumption, approximately half of the sample (47.1%) consumed their medications with meals or used in a range less than the recommended time of 30 minutes before a meal or 2 hours after the same.

DISCUSSION

In most cases, the progression of Parkinson's disease is accompanied with consequent loss of weight (1, 7, 11, 18, 19). The weight loss is continuous and may begin before the disease diagnosis (1). This can occur due to motor difficulties and increased energy consumption caused by the disease, resulting in a malnutrition status in these patients (18).

Among evaluated patients, 53% had nutritional risk according to the MNA. As in other studies with PD (7, 19), our sample showed no risk of malnutrition by BMI classification. However, these patients (table 1) have a lower BMI compared with healthy elderly subjects from the same region of the country (BMI = 28.9 kg /m²)(20).Therefore, the BMI elderly rates have limitations and may not be used exclusively, since this indicator assesses only the body mass without defining its distribution (21). This way, for these patients is important to use other nutritional parameter as a MNA, since it is a more sensitive method than BMI and anthropometry for assessing the nutritional status, since it evaluates the individual in global terms and can identify more accurately the nutritional risk in this population.

Energy and protein consumption profile of PD patients was also evaluated and compared to the southern population of the country and other related studies. According to the Household Budget Survey (Pesquisa de Orçamentos Fami-

TABLE 1

Nutritional profile of PD patients in ambulatory treatment

	Men (n=20)	Women (n=14)	Total (n=34)
Age (years)	67.2 ± 9.3	64.6 ± 9.7	66.2 ± 9.4
Disease duration (years)	5.6 ± 4.3	7.1 ± 5.6	6.2 ± 4.9
Weigh (kg)	69.7 ± 9.7	64.3 ± 12.1	67.5 ± 10.9
Height (m)	1.67 ± 0.1	1.56 ± 0.1	1.62 ± 0.1
BMI (kg/m ²)	25.0 ± 3.6	26.6 ± 4.9	25.6 ± 4.2
Nutritional status* :			
at risk of malnutrition	11 (55.0%)	7 (50.0%)	18 (52.9%)
without risk of malnutrition	9 (45.0%)	7 (50.0%)	16 (47.1%)

Average ± standard deviation. * number of patients and absolute (%).

liars - POF) 2008/2009(22), elderly males, consumed 1774 kcal energy/day and 75 g protein/day (16.9% of energy as protein), similar to the study population as well as the found by Lorefält et al. (7), 1743.7 kcal/day. The women in this age group consume energy 1484 kcal/day and 56.2 g protein/day (15.2% of energy as protein), smaller than the sample. These differ when compared to Paré et al.(19) (energy 2351 kcal/day and 83g protein/day, male and energy 1975kcal / day and 71 g protein/day, females) and Marczewska et al. (23) (2360 kcal/day and 84 g/day) that showed energy and total protein consumption greater than the patients of this study. However, energy consumption in the studied population is appropriate.

Studies were conducted to evaluate the PD patients diet and the interference in the pharmacologic therapy (4, 9, 19, 24, 25). However, the number of different methodologies and the variety of sample populations do not provide any conclusive evidence to which is the best nutritional therapy for these patients in order to be able to relate the use of levodopa and other drugs (4, 6, 8, 10, 18).

After administration, levodopa is absorbed in the first portion of the small intestine by a saturable active transport mechanism which is also used by some aminoacids (1, 5, 10, 18, 19, 23). Furthermore, the same aminoacids compete with the drug by active transport in the blood-brain barrier (5, 25, 26). Studies show that a diet high protein consumption may reduce the levodopa bioavailability, showing the interaction drug/food (8, 24, 25, 27-29). However, Robertson et al.(30) ensure that there is no amino acids interference in the intestinal absorption of levodopa, and suggest that the interference occurs only in competing for blood brain barrier. It is similar to study of Simon et al. (26) which asserts that the protein may have a little effect on the intestine absorption of levodopa and it is most likely the aminoacid/drug competition to entry into the CNS.

In Pare et al. (19), it was observed that a diet with protein and energy content similar to the usual but with a change in protein amount during the day, decreases the motor fluctuations symptoms that may be caused by levodopa use. Besides this, other studies have demonstrated that reduction in protein intake throughout the day can reduce the effects

of periods off (9, 19), which are periods of motor fluctuations in a patient that is not answering to medication (9). Even if these fluctuations can be unpredictable and spontaneous, they often become worse after meals(18). A great number of related studies argue that nutritional advice on protein intake can improve the levodopa kinetic profile, and therefore its therapeutic efficacy (1, 9, 10, 18, 19, 24, 29). The daily protein amount ingested and its distribution throughout the day are among the dietary recommendations found in the literature for reducing this influence. Studies recommend that consumption of protein for PD patients treated with levodopa is within ± 0.8 g/kg/day (1, 10, 24, 25). However, data confirm that PD patients consume over 50% of the recommended protein g/kg/day (1.2 vs 0.8 g)(18, 23), similar to those found in our study. But, before indicating a protein-restricted diet, which may compromise energy and other nutrients intake (18, 19, 31), must consider whether this intervention is needed. Therefore, if the patient does not have motor fluctuations with levodopa, there is no justification for prescribing a diet with reduction of protein (19). In this work, it have not been evaluated motor fluctuations in patients or considered the stage of the disease in the population. The lack of these data limited discussions of possible levodopa administration and protein intake in patients.

Another relevant diet advice is to adequate the diet with the normal percentage of protein in energy intake (15% of energy as protein) and that this value is valid for patients with early stage of disease. For patients in advanced PD stages can decrease the percent daily for 10% of energy as protein (1).

Furthermore, to reduce the effects of diet on levodopa is directed that PD patients decrease protein intake during the day and prioritize by night (1, 19, 31). This orientation is opposed to feeding behavior described in this work, in which the patients consume most of the dietary protein until to afternoon snack.

Besides the amount of protein in the diet and its distribution throughout the day, another care refers to the time before and after the meal that the drug should be ingested to improve the absorption (25, 28). In levodopa use, the time for drug administration should be at least half hour before a

TABLE 2

Average consumption of energy and protein of PD patients, by calculating the 3-day food record

Men n=20)	Women (n=14)	Total (n=34)	
Total energy (kcal/day)	1797.1 \pm 581.4	1711.9 \pm 270.4	1762.0 \pm 474.6
Protein total daily (g)	77.2 \pm 21.1	62.0 \pm 8.3	70.9 \pm 18.5
Protein total/daily (%)*	17.9	14.7	16.6
Protein g/kg/day**	1.1 \pm 0.3	1.0 \pm 0.3	1.1 \pm 0.3
Protein g/meal			
Breakfast	11.7 \pm 5.5	9.3 \pm 3.0	10.7 \pm 4.7
Morning snack	1.5 \pm 3.7	1.2 \pm 1.5	1.4 \pm 3.0
Lunch	33.2 \pm 10.7	25.2 \pm 8.6	29.9 \pm 10.5
Afternoon snack	7.8 \pm 5.1	7.2 \pm 4.7	7.5 \pm 4.9
Dinner	22.4 \pm 11.7	17.9 \pm 6.7	20.5 \pm 10.0
Supper	0.2 \pm 0.8	0.5 \pm 1.3	0.3 \pm 1.0

Average \pm standard deviation. * Absolute percentage figure. ** KS = -0,1459; IC = 0,97-1,2 g/kg.

meal (1, 18), and after a meal must occur a minimum break of two hours (25). In this study, 47% of patients consumed some food along with medicine. In the literature this practice is related to the need to prevent some symptoms such as nausea and discomfort(10). The use of low protein content products for renal patients is an alternative for patients who need to redistribute the protein consumption during the day (18, 31).

Rich-protein meals may interfere with the absorption of levodopa, but is not scientifically established the effectiveness of applying a low-protein diet for these patients (10, 26). Anyway, it is recommended a balanced diet and preferably with the protein restriction during a day, controlling the time of drug administration and ingestion of diet to ensure maximization of drug absorption (1, 23, 29). Therefore, it is necessary to know and guide the schedules and intervals of medication intake in relation to meals (23, 28).

According to the recommendations described in the literature about the protein intake and pharmacological treatment of PD, our patients consume more protein than the recommendation for this disorder, there is a higher concentration of this nutrient during the day diet, and half of the sample takes the drugs for the treatment of PD with the meal.

In order to improve the proposed treatment, additional studies are needed to evaluate the real effect of protein intake on levodopa bioavailability in patients at different stages of Parkinson's disease.

RESUMEN

La levodopa es el principal tratamiento farmacológico para la enfermedad de Parkinson, sin embargo, la proteína de la dieta puede comprometer su eficacia. El objetivo de este estudio fue investigar la ingesta de proteínas y el uso de la levodopa en pacientes con enfermedad de Parkinson tratados en régimen ambulatorio, 34 pacientes fueron evaluados. Evaluación de la ingesta de alimentos por los registros, tomas de 1762 kcal/día, 70.9 g/día, el 16,6% del total de energía y 1.1 g/kg/día de energía y proteína, respectivamente, y que la ingesta de proteínas durante el día era 70,4% del total de proteínas diario. Todos los pacientes estaban tomando levodopa y 47,1% consumían sus medicamentos con las comidas. Se concluyó que, según las recomendaciones para la enfermedad de Parkinson, los pacientes estudiados consumían una dieta rica en proteínas y con una mayor concentración de este nutriente durante el día. Aproximadamente la mitad de la muestra ingiere los medicamentos con la comida, costumbre que puede afectar el tratamiento farmacológico de la enfermedad.

Palabras clave: enfermedades neurodegenerativas; dieta hiperproteica; interacciones fármaco-alimento; carbidopa.

REFERENCES

1. Barichella M, Cereda E, Pezzoli G. Major nutritional issues in the management of Parkinson's disease. *Mov Disord* 2009; 24: 1881-92.
2. Riederer P, Gerlach M, Muller T, Reichmann H. Relating mode of action to clinical practice: dopaminergic agents in Parkinson's disease. *Parkinsonism Relat Disord* 2007; 13: 466-79.
3. Toulouse A, Sullivan AM. Progress in Parkinson's disease-where do we stand? *Prog Neurobiol* 2008; 85: 376-92.
4. Juri CC, Chaná CP. Levodopa en la enfermedad de Parkinson: ¿Qué hemos aprendido? *Rev Med Chil* 2006; 134: 893-901.

5. Cushing ML, Traviss KA, Calne SM. Parkinson's disease: implications for nutritional care. *Can J Diet Pract Res* 2002; 63: 81-7.
6. Khor SP, Hsu A. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. *Curr Clin Pharmacol* 2007; 2: 234-43.
7. Lorefalt B, Granerus AK, Unosson M. Avoidance of solid food in weight losing older patients with Parkinson's disease. *J Clin Nurs* 2006; 15: 1404-12.
8. Mattos JPD, Mattos VMDBC. Novos agonistas dopaminérgicos. *Arq Neuro-Psiquiatr* 1999; 57: 329-32.
9. Olanow CW, Watts RL, Koller WC. An algorithm (decision tree) for the management of Parkinson's disease (2001): treatment guidelines. *Neurology* 2001; 56: S1-S8.
10. Cereda E, Barichella M, Pedrolli C, Pezzoli G. Low-protein and protein-redistribution diets for Parkinson's disease patients with motor fluctuations: a systematic review. *Mov Disord* 2010; 25: 2021-34.
11. Moura MRL, Reyes FGR. Interação fármaco-nutriente: uma revisão. *Rev Nutr* 2002; 15: 223-238.
12. Guigoz Y, Vellas B, Garry PJ. Assessing the nutritional status of the elderly: The Mini Nutritional Assessment as part of the geriatric evaluation. *Nutr Rev* 1996; 54: S59-65.
13. Lipschitz DA. Screening for nutritional status in the elderly. *Prim Care* 1994; 21: 55-67.
14. Frisancho AR. Anthropometric Standards: An interactive nutritional Reference of Body Size and Body Composition for Children and Adults. 4th Ed. Arbor: The University of Michigan Press, 2011.
15. Fisberg MR, Marcuioni DML, Slater B, Martini LA. Inquéritos Alimentares: Métodos e Bases Científicas. 2nd Ed. Barueri: Manole, 2005.
16. Philippi ST. Tabela de composição de alimentos: suporte para decisão nutricional. 2nd Ed. São Paulo: Coronário, 2002.
17. Pinheiro ABV, Lacerda EMA, Benzecry EH, Gomes MCS, Costa VM. Tabela para avaliação de consumo alimentar em medidas caseiras. 5th Ed. São Paulo: Atheneu, 2005.
18. Cereda E, Barichella M, Pezzoli G. Controlled-protein dietary regimens for Parkinson's disease. *Nutr Neurosci* 2010; 13: 29-32.
19. Pare S, Barr SI, Ross SE. Effect of daytime protein restriction on nutrient intakes of free-living Parkinson's disease patients. *Am J Clin Nutr* 1992; 55: 701-7.
20. Piccoli JCI, Quevedo DMd, Santos GAd, Ferrareze ME, Gluher A. Coordenação global, equilíbrio, índice de massa corporal e nível de atividade física: um estudo correlacional em idosos de Ivoti, RS, Brasil. *Rev Brasileira Geriatria Gerontol* 2012; 15: 209-22.
21. Cervi A, Franceschini SdCC, Priore SE. Análise crítica do uso do índice de massa corporal para idosos. *Rev Nutr* 2005; 18: 765-75.
22. Brasil. Instituto Brasileiro de Geografia e Estatística. Pesquisa de Orçamentos Familiares (POF) 2008-2009 – Análise do Consumo Alimentar Pessoal do Brasil. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística – IBGE; 2011.
23. Marczevska A, De Notaris R, Sieri S, Barichella M, Fusconi E, Pezzoli G. Protein intake in Parkinsonian patients using the EPIC food frequency questionnaire. *Mov Disord* 2006; 21: 1229-31.
24. Juncos JL, Fabbri G, Mouradian MM, Serrati C, Chase TN. Dietary influences on the antiparkinsonian response to levodopa. *Arch Neurol* 1987; 44: 1003-5.
25. Contin M, Riva R, Martinelli P, Albani F, Baruzzi A. Effect

- of meal timing on the kinetic-dynamic profile of levodopa/carbidopa controlled release [corrected] in parkinsonian patients. *Eur J Clin Pharmacol* 1998; 54: 303-8.
26. Simon N, Gantcheva R, Bruguerolle B, Viallet F. The effects of a normal protein diet on levodopa plasma kinetics in advanced Parkinson's disease. *Parkinsonism Relat Disord* 2004; 10: 137-42.
 27. Kempster PA, Wahlqvist ML. Dietary factors in the management of Parkinson's disease. *Nutr Rev* 1994; 52: 51-8.
 28. Crevoisier C, Zerr P, Calvi-Gries F, Nilsen T. Effects of food on the pharmacokinetics of levodopa in a dual-release formulation. *Eur J Pharm Biopharm* 2003; 55: 71-6.
 29. Carter JH, Nutt JG, Woodward WR, Hatcher LF, Trotman TL. Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease. *Neurology* 1989; 39: 552-6.
 30. Robertson DR, Higginson I, Macklin BS, Renwick AG, Waller DG, George CF. The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. *Br J Clin Pharmacol* 1991; 31: 413-7.
 31. Barichella M, Marczevska A, De Notaris R, et al. Special low-protein foods ameliorate postprandial off in patients with advanced Parkinson's disease. *Mov Disord* 2006; 21: 1682-7.