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Hydrosoluble fiber (*Plantago ovata* husk) and levodopa II: Experimental study of the pharmacokinetic interaction in the presence of carbidopa

Nelida Fernandez*, Demetrio Carriedo, Matilde Sierra, M. Jose Diez, Ana Sahagun, Angela Calle, Aranzazu Gonzalez, Juan J. Garcia

Area de Farmacologia, Universidad de Leon, 24071 Leon, Spain

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Abstract

Levodopa combined with carbidopa constitutes one of the most frequent medication in the treatment of Parkinson's disease. *Plantago ovata* husk (water-soluble fiber) improves levodopa absorption conditions, but when this drug is administered with carbidopa, fiber could reduce its effectiveness. The purpose of this study is to investigate whether the presence of *P. ovata* husk modifies in rabbits the bioavailability and other pharmacokinetic parameters of levodopa (20 mg/kg) when administered by the oral route with carbidopa (5 mg/kg). We have also studied whether pharmacokinetic modifications are fiber–dose dependent (100 and 400 mg/kg). When levodopa and carbidopa were administered with 100 mg/kg *P. ovata* husk, the value of AUC for levodopa diminishes 29.7% (sign, $n=6$, $P<0.05$) and C_{max} 28.1% (sign, $n=6$, $P<0.05$) in relation to the values obtained when these drugs were administered without fiber. If the dose of fiber was 400 mg/kg, the decrease was smaller: 20.4% for AUC (no significant difference) and 24.6% for C_{max} (sign, $n=6$, $P<0.05$), that may indicate an inhibitory action of AADC by the fiber or any of its partial hydrolysis products. On the other hand, since certain time on, levodopa concentrations are always higher in the groups that receive fiber: 210 min with 100 mg/kg and 150 min with 400 mg/kg. The administration of *P. ovata* husk with levodopa/carbidopa to patients with Parkinson disease could be beneficial and in particular in those patients who also suffer constipation due to an improvement of levodopa kinetic profile with higher final concentrations, a longer plasma half-life and lower C_{max}.

Keywords: Levodopa; Carbidopa; *Plantago ovata* husk; Pharmacokinetics; Rabbits; Fiber

1. Introduction

Levodopa combined with a peripheral inhibitor of aromatic L-amino acid decarboxylase (benserazide, carbidopa) constitutes the most frequent medication in the treatment of Parkinson's disease (Agid et al., 2002).

Following oral administration, levodopa is extensively metabolised to dopamine by the enzyme aromatic amino acid decarboxylase (AADC) in the gut (Andersson et al., 1975) with approximately 30% of a levodopa dose reaching the systemic circulation.

Carbidopa administration markedly reduces both the required levodopa therapeutic dosage and the severity of dopamine-mediated gastrointestinal and cardiovascular adverse effects (Pinder et al., 1976).

There is growing recognition that gastrointestinal dysfunction is common in Parkinson's disease. Virtually all parts of the gastrointestinal tract can be affected, in some cases early in the disease course. Bowel dysfunction can consist of both slowed colonic transit with consequent reduced bowel-movement frequency, and difficulty with the act of defecation itself with excessive straining and incomplete emptying. Recognition of these gastrointestinal complications can lead to earlier and potentially more effective therapeutic intervention.

Prokinectic drugs may help reduce the symptoms of gastrointestinal dismotility, but the side effects preclude their prolonged use (Garnett, 1996). Fiber therapy could be employed to reduce the symptoms of gastrointestinal

* Corresponding author. Tel.: +34 9 87 29 15 28; fax: +34 9 87 29 12 52.
E-mail address: dftnfm@unileon.es (N. Fernandez).

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motility disorders, because it accelerates stool transit in the small as well as in the large intestine and fluids work in conjunction with fiber to make stools soft, bulky and easier to pass.

Plantago ovata husk improves levodopa absorption conditions (Fernández et al., 2003), but when this drug is administered with carbidopa, fiber could reduce the effectiveness of this AADC inhibitor.

The purpose of the present study is to establish the influence of *P. ovata* husk in the bioavailability and other pharmacokinetic parameters of levodopa when administered to rabbits by the oral route with carbidopa and the fiber. We also evaluate whether pharmacokinetic modifications are fiber–dose dependent.

2. Experimental procedures

2.1. Study design

To carry out the study, eighteen healthy New Zealand white rabbits with a body weight range of 2.7–3.3 kg were used. The environmental conditions were: constant humidity (55% ± 10%), temperature (19 ± 2 °C) and 12 h light–12 h dark cycle. The animals were housed in individual metal cages, which allowed the isolation of faeces in a lower container to avoid coprophagia. Rabbits were maintained under these conditions at least 1 week before assay, with free access to water and standard laboratory chow.

The rabbits were randomly divided into three groups of 6 rabbits each. All the animals of the first group received 20:5 mg/kg of levodopa/carbidopa (Sinemet®) by the oral route using a gavage needle.

On the other hand, the rabbits of the second and third groups also received *P. ovata* husk (Plantaben®, Madaus, Barcelona, Spain) immediately before levodopa/carbidopa administration at two different doses: 100 mg/kg (second group) and 400 mg/kg (third group). The fiber was administered dispersed in water by gastric intubation. A total of 50 ml water was used for fiber administration and cannula cleaning.

Blood samples were obtained from the left carotid artery previously cannulated with a silicone catheter, (Silastic® Medical-grade tubing, 1.02 mm (inner diameter) × 2.16 mm (outer diameter)). The catheters were placed under anaesthesia with sodium pentobarbital (Barcia, Madrid, Spain), 30 mg/kg, i.v. Drug administration was carried out after total recovery from anaesthesia was achieved.

Blood samples (3 ml) were collected through the cannula into heparinized containers before, and at 5, 10, 20, 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 min after levodopa/carbidopa, with and without fiber, oral administration. Immediately after collection, plasma was separated by centrifugation and stored at −20 °C until analyzed. Levodopa extraction from plasma samples was carried out by using a catecholamine kit (Chromsystems®) and was quantitated by HPLC with electrochemical detection. Neither heparin nor pentobarbital interfered on the assay.

2.2. Pharmacokinetic studies

Pharmacokinetic analysis was performed based on a non-compartmental description of the data observed.

The WinNonlin computer program and formulae described by Gibaldi and Perrier (1982) were used to calculate the model-independent pharmacokinetic parameters. Maximum plasma levodopa concentration (C_{max}) and the time to reach maximum concentration (t_{max}) were read directly from the individual plasma concentration–time curves.

2.3. Statistical evaluation

All pharmacokinetic parameters were calculated for each animal and the data presented as arithmetic mean ± standard deviation (mean ± SD). Data were analyzed by analyses of variance (ANOVA) and the Duncan's test was used to evaluate differences between data sets. When the data were not normal or there was not uniformity in the variance, Kruskal–Wallis test was used, and when the results were significant, Wilcoxon test with Bonferroni correction was used to assess differences between data sets. $P \leq 0.05$ was used as the level of significance for all analyses.

3. Results

The plot of mean plasma levodopa concentration as a function of time after oral administration for the three groups studied are shown in Fig. 1 (levodopa/carbidopa alone and in the presence of 100 and 400 mg/kg of *P. ovata* husk).

The non-compartmental pharmacokinetic parameters obtained after the administration of 20:5 mg/kg levodopa/carbidopa and in the presence of 100 and 400 mg/kg of *P. ovata* husk are summarized in Tables 1, 2 and 3, respectively.

When levodopa and carbidopa were administered with 100 mg/kg *P. ovata* husk, the value of AUC for levodopa diminishes 29.7% (sign, $n=6$, $P<0.05$) and C_{max} 28.1% (sign, $n=6$, $P<0.05$) in relation to the values obtained when levodopa and carbidopa were administered without fiber. If the dose of fiber administered was 400 mg/kg, the decrease was smaller: 20.4% for AUC (no significant difference) and 24.6% for C_{max} (sign, $n=6$, $P<0.05$).

Nevertheless, the amount of levodopa available from 210 min on was 79.2% higher in the presence of 100 mg/kg fiber than when levodopa and carbidopa were administered without fiber. Likewise, when the dose of fiber was 400 mg/kg, this percentage was 20.3% but concentrations increased from 150 min on.

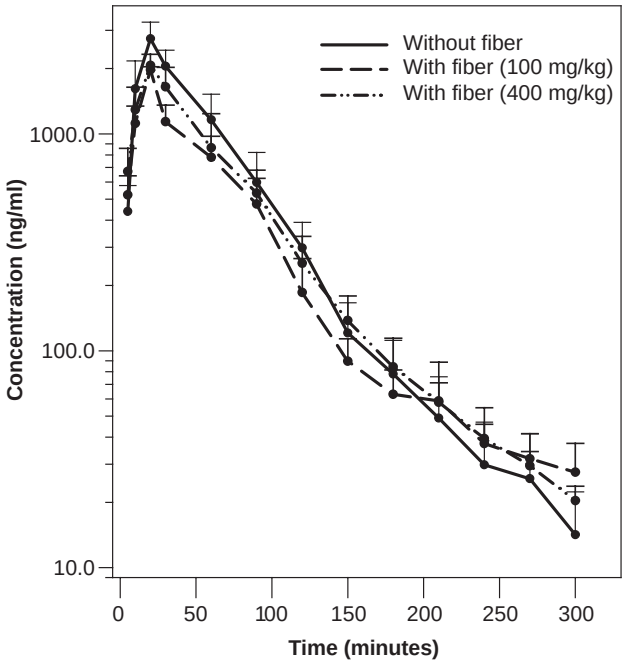

Fig. 1. Mean plasma concentrations of levodopa in rabbits after oral administration of 20:5 mg/kg levodopa/carbidopa without fiber and in the presence of *P. ovata* husk (100 or 400 mg/kg).

The value of clearance obtained after levodopa/carbidopa administration (134 ± 27.0 ml kg^{-1} min^{-1}), is lower than the obtained when 100 mg/kg fiber (188 ± 32.1 ml kg^{-1} min^{-1}, (sign, $n=6$, $P<0.05$)) or 400 mg/kg *P. ovata* husk (161 ± 31.6 ml kg^{-1} min^{-1}, no significant differences) were given. However, the differences observed in Cl as well as in V_{ss} values can be attributed to variations in F.

4. Discussion

The evaluation of the pharmacokinetics of levodopa is complicated by the presence of carbidopa, since carbidopa influences both the absorption and the systemic elimination of levodopa (Huebert et al., 1986, Leppert et al., 1988, Bredberg et al., 1994).

Following oral administration, and when levodopa is administered with carbidopa, levodopa bioavailability is nearly tripled and C_{max} is 1.93 times greater (Fernández et al., 2003). This result is in accordance with those reported by other authors (Hietala et al., 1979, Linden, 1980).

The value obtained for t_{max} in the three groups studied (20 min) is the same as the obtained when levodopa is administered with fiber and without carbidopa (Fernández et al., 2003). This value is similar to that reported by Deleu et al. (1991) in dogs. The values found in men ranged from 30 min to 2 h (Bredberg et al., 1990, Grahnen et al., 1992, Contin et al., 1993).

Levodopa half-life is short, even with concomitant intake of AADC inhibitors, ranging from 0.7 to 1.4 h in Parkinsonian patients undergoing long term treatment (Nelson et al., 1989, Bredberg et al., 1990, Contin et al., 1990). The value obtained for the plasma elimination half-life of levodopa when was orally administered with carbidopa (51.4 min) is similar to the reported by Grange et al. (2001) in rats after oral administration of levodopa with benserazide (49 min).

Dietary factors can modify the rate and extent of levodopa absorption. It is well established, for example, that the absorption of this compound can be reduced or retarded by concomitant food intake (Rivera-Calimlim et al., 1970; Nutt et al., 1984).

The stomach has a very limited capacity to absorb levodopa, but can decarboxylate this drug (Rivera-Calimlim et al., 1970). Thus, the major role of the stomach is as a valve, controlling the delivery of an ingested levodopa dose to the intestine absorptive sites (Nutt and Fellman, 1984). *P. ovata* husk can delay gastric emptying and retain part of the dose of levodopa administered. This would explain the lower initial concentrations of levodopa when fiber is administered. The decrease in AUC may be due to a retention of part of the dose of carbidopa administered by the fiber, diminishing initially its effectiveness to inhibit the enzyme AADC, because when levodopa is administered with 100 mg/kg of *P. ovata* husk (Fernández et al., 2003) AUC is not modified.

Table 1
Pharmacokinetic parameters obtained by non-compartmental analysis in rabbits after oral administration of 20:5 mg/kg levodopa/carbidopa

Parameters	Animal						$\bar{x} \pm s$	CV (%)
	1	2	3	4	5	6		
λ (min^{-1})	0.0158	0.0168	0.0096	0.0131	0.0136	0.0147	0.0139 ± 0.0025	18.12
AUC (μg min ml^{-1})	127	199	120	141	152	190	155 ± 32.8	21.20
C_{max} (μg ml^{-1})	2.82	3.03	2.41	2.43	2.16	3.62	2.74 ± 0.53	19.30
t_{max} (min)	20.0	20.0	20.0	20.0	20.0	20.0	20.0 ± 0.00	0.00
Cl/F (ml kg^{-1} min^{-1})	157	101	167	142	132	105	134 ± 27.0	20.17
V_a/F (l kg^{-1})	9.95	5.99	17.4	10.8	9.67	7.15	10.2 ± 3.99	39.23
V_{ss}/F (l kg^{-1})	6.85	5.38	10.7	9.38	8.36	5.78	7.74 ± 2.08	26.94
$t_{1/2\lambda}$ (min)	43.9	41.3	72.2	52.9	51.0	47.1	51.4 ± 11.1	21.54
AUMC (μg min^2 ml^{-1})	5543	10,647	7641	9317	9670	10,468	8881 ± 1956	22.02
MRT (min)	43.6	53.5	63.8	66.1	63.6	55.0	57.6 ± 8.56	14.85

Table 2
Pharmacokinetic parameters obtained by non-compartmental analysis in rabbits after oral administration of 20 : 5 mg/kg levodopa / carbidopa in the presence of fiber (100 mg/kg)

Parameters	Animal						$\bar{x} \pm s$	CV (%)
	1	2	3	4	5	6		
λ (min^{-1})	0.0073	0.0091	0.0094	0.0081	0.0082	0.0077	0.0083 ± 0.0008	9.73
AUC ($\mu g\ min\ ml^{-1}$)	101	81.5	127	107	112	124	109 ± 16.7	15.31
C_{max} ($\mu g\ ml^{-1}$)	1.97	2.04	1.90	2.00	2.04	1.89	1.97 ± 0.07	3.39
t_{max} (min)	20.0	20.0	20.0	20.0	20.0	20.0	20.0 ± 0.00	0.00
Cl/F ($ml\ kg^{-1}\ min^{-1}$)	198	245	157	187	178	161	188 ± 32.1	17.07
V_a/F ($l\ kg^{-1}$)	27.1	27.0	16.7	23.1	21.7	21.0	22.8 ± 3.94	17.29
V_{ss}/F ($l\ kg^{-1}$)	13.5	17.1	10.5	14.7	10.2	13.5	13.2 ± 2.60	19.65
$t_{1/2\lambda}$ (min)	94.9	76.2	73.7	85.6	84.5	90.0	84.2 ± 8.07	9.58
AUMC ($\mu g\ min^2\ ml^{-1}$)	6877	5683	8499	8363	6422	10,400	7707 ± 1717	22.28
MRT (min)	68.1	69.7	66.8	78.3	57.2	83.9	70.7 ± 9.35	13.24

When 100 mg/kg of *P. ovata* husk are administered with levodopa/carbidopa, the extent of levodopa absorbed is a 29.7% lower. However, when the dose of fiber is increased to 400 mg/kg, the reduction in the extent of levodopa absorbed is lower (20.4%). We think that *P. ovata* husk, or any product of its partial hydrolysis, could inhibit the enzyme AADC, as it has been demonstrated for other enzymes (Isaksson et al., 1982, Hansen, 1986, Leng-Peschlow, 1991), being this effect more important with the higher dose of fiber.

On the other hand, *P. ovata* husk administration can reduce the severity of dopamine-mediated gastrointestinal and cardiovascular adverse effects (Pinder et al., 1976) enhancing the results of levodopa/carbidopa treatment by improving levodopa kinetic profile with a longer plasma half-life and lower C_{max}. Variation in levodopa concentrations is the determining factor for motor fluctuations also in patients clinically optimized with combinations of dopamine agonists and enzyme inhibitors (Nyholm et al., 2002).

The "wearing off" phenomenon can be associated with a "negative" Parkinsonism-exacerbating action of levodopa at low, subtherapeutic or around therapeutic plasma concentrations (Paalzow and Paalzow, 1986). As the levodopa therapeutic response grows more complicated, a variety of diskynesias often appear (Nutt, 1990) which may be related to both high levodopa "peak" and low subtherapeutic plasma concentrations (Sage et al., 1991).

According to Djaldetti et al. (1995) the "delayed-on" (prolonged latencies to onset) phenomenon and "non-on" (treatment failure) phenomenon are related to alterations of the gastrointestinal transit time and absorption of levodopa. Several authors have indicated that the induction of on/off phenomena and dyskinesias may be the result of an active process of adaptation to variations in brain and plasma levodopa levels. In this way, when levodopa concentrations are maintained at a constant level by intravenous infusion dyskinesias and fluctuations are greatly reduced (Mouradian et al., 1990; Chase et al., 1994).

We think that *P. ovata* husk offers interesting perspectives to be administered to patients with Parkinson disease and that its effect would be even more beneficial in those patients who also suffer constipation, although further studies administering the drugs employed in this study

Table 3
Pharmacokinetic parameters obtained by non-compartmental analysis in rabbits after oral administration of 20 : 5 mg/kg levodopa / carbidopa in the presence of fiber (400 mg/kg)

Parameters	Animal						$\bar{x} \pm s$	CV (%)
	1	2	3	4	5	6		
λ (min^{-1})[c,d]	0.0097	0.0138	0.0151	0.0129	0.0101	0.0121	0.0123 ± 0.0021	17.11
AUC ($\mu g\ min\ ml^{-1}$)[c]	97.0	128	108	173	134	132	129 ± 26.4	20.50
C_{max} ($\mu g\ ml^{-1}$)[a,b]	1.73	2.11	1.85	2.46	2.21	2.05	2.07 ± 0.26	12.40
t_{max} (min)	20.0	20.0	20.0	20.0	20.0	20.0	20.0 ± 0.00	0.00
Cl/F ($ml\ kg^{-1}\ min^{-1}$)[c]	206	156	186	115	149	152	161 ± 31.6	19.62
V_a/F ($l\ kg^{-1}$)[c,d]	21.3	11.3	12.3	8.95	14.8	12.6	13.5 ± 4.23	31.30
V_{ss}/F ($l\ kg^{-1}$)[c]	13.4	9.17	13.7	7.50	8.88	8.98	10.3 ± 2.61	25.37
$t_{1/2\lambda}$ (min)[c,d]	71.4	50.2	45.9	53.7	68.6	57.3	57.9 ± 10.2	17.61
AUMC ($\mu g\ min^2\ ml^{-1}$)	6305	7496	7932	11,268	7981	7781	8127 ± 1659	20.41
MRT (min)[c]	65.0	58.6	73.7	65.0	59.5	59.1	63.5 ± 5.77	9.09

Significant differences between levodopa/carbidopa and levodopa/carbidopa + fiber (100 mg/kg) groups: [a]Wilcoxon modified test, [c]Duncan test, $P \leq 0.05$. Significant differences between levodopa/carbidopa and levodopa/carbidopa + fiber (400 mg/kg) groups: [b]Wilcoxon modified test. Significant differences between levodopa/carbidopa + fiber (100 mg/kg) and levodopa/carbidopa + fiber (400 mg/kg) groups: [d]Duncan test, $P \leq 0.05$.

during prolonged periods of time, to stabilize the inhibitory action of carbidopa and the effect of *P. ovata* husk on this AADC inhibitor, are necessary.

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