Expert Opinion

Effects of dietary factors on levodopa pharmacokinetics

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Importance of the field: Levodopa is the most effective treatment for Parkinson's disease, so it is important to understand the pharmacokinetic and pharmacodynamic features of this drug. Considering the pharmacokinetics of levodopa and the factors that can modify it are essential for the clinician when prescribing levodopa products in order to maximize their therapeutic effects.

Areas covered in this review: This paper reviews the studies carried out evaluating the interaction between levodopa and dietary factors.

What the reader will gain: The reader will gain a greater understanding of the different dietary factors that can affect levodopa pharmacokinetics and, thus, the therapeutic response that is obtained with this drug in several situations.

Take home message: An understanding of the pharmacokinetics of any drug is crucial for the establishment of its optimal therapeutic regimen, but this assumes a special importance with levodopa, due to its extensive presystemic metabolism, rapid absorption in the proximal small intestine and short plasma half-life. Major problems with levodopa treatment are the fluctuations in clinical response experienced in patients with advanced Parkinson's disease that sometimes are related to the peripheral pharmacokinetics of levodopa. Studies of levodopa interactions are very important to improve patient response to this drug.

Keywords: dietary factors, interaction, levodopa, pharmacokinetics

Expert Opin. Drug Metab. Toxicol. (2010) 6(5):633-642

1. Introduction

Parkinson's disease is characterized by the progressive degeneration of the nigrostriatal dopamine pathway. Cell bodies of dopamine-releasing neurons are located in the substantia nigra, while the cells project to the striatum where nerve terminals release the neurotransmitter, dopamine [1-5]. Striatal dopamine deficiency in Parkinson's disease was first described in 1960. In 1961, levodopa was tried in Parkinson's disease patients [6], but its effectiveness in Parkinson's disease was finally established in 1967 when Cotzias and colleagues reported dramatic improvement in Parkinson's disease patients with oral administration of levodopa in increasing amounts over long periods [7].

The introduction of levodopa in the 1960s revolutionized the treatment of Parkinson's disease, and it continues to be the most effective symptomatic therapy [8-10]. Levodopa improves most parkinsonian symptoms and is associated with an apparent decrease in mortality rate. However, levodopa usage is also associated with distressing side effects, such as uncontrollable movements, that compromise treatment [11-14]. Response fluctuations and its wide distribution throughout the body is the major obstacle when levodopa is administered orally. Together with a poor blood–brain transport, there is only ~ 1% of the administered dose available to the brain [15-17]. Due to rapid absorption and disposition of levodopa, its plasma

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Article highlights.

- Levodopa is the most effective treatment for Parkinson's disease; so it is important to understand the pharmacokinetic and pharmacodynamic features of this drug.
- Major problems with levodopa treatment are the fluctuations in clinical response experienced in patients with advanced Parkinson's disease. Some of these fluctuations (e.g., wearing-off, on-off) in motor performance are related to the peripheral pharmacokinetics of levodopa.
- One of the major problems in the daily life of patients with Parkinson's disease is gastrointestinal dysfunction, especially constipation. Constipation is included among the non-motor symptoms, which are often poorly recognized and inadequately treated in contrast with the dopaminergic symptoms of the disease, for which treatment is available.
- The results obtained in patients with Parkinson's disease indicate that aromatic amino acids interfere in the absorption and brain penetration of levodopa, and modifying protein intake improves the quality of the response.
- Other dietary factors such as the administration of fiber or ascorbic acid conduced to an improvement of several pharmacokinetic parameters of levodopa.

This box summarizes key points contained in the article.

concentrations rapidly rise and fall after drug intake [18-20]. In the early 1970s, the advantages of adding a dopa decarboxylase inhibitor to treatment were discovered, and the first levodopa combination, carbidopa/levodopa, became commercially available in 1975. Carbidopa is a peripheral decarboxylase inhibitor with little or no pharmacological activity when given alone in usual doses. It inhibits the peripheral decarboxylation of levodopa to dopamine and as, unlike levodopa, it does not cross the blood–brain barrier, effective brain concentrations of dopamine are produced with lower doses of levodopa. At the same time, reduced peripheral formation of dopamine reduces peripheral side effects, notably, nausea and vomiting and cardiac arrhythmias, although the dyskinesias and mental effects associated with levodopa therapy tend to develop earlier [21-23]. Another peripheral decarboxylase inhibitor usually used to increase the central availability of levodopa is benserazide [24].

A further development was the introduction of catechol-*O*-methyltransferase (COMT) inhibitors, an enzyme that also metabolizes levodopa. The addition of these inhibitors, entacapone or tolcapone, decreases peripheral levodopa degradation to 3-*O*-methyldopa and thus increases the delivery of levodopa to the brain, prolonging its half-life in the periphery [25-28]. It has been proved that adjunction of the COMT inhibitor entacapone to levodopa/carbidopa improves motor symptoms in patients with Parkinson's disease [26,29,30] probably due to a hypothetically increased dopamine occurrence at the prefrontal cortex, which guides human behavior. It was also demonstrated that entacapone did not influence gastric emptying [30].

Major problems with levodopa treatment are the fluctuations in clinical response experienced in patients with advanced Parkinson's disease. Some of these fluctuations (e.g., wearing-off, on-off) in motor performance are related to the peripheral pharmacokinetics of levodopa [18,31-34]. Pulsatile simulation of striatal dopamine receptors induces molecular and neurophysiological changes in striatal neurons that are associated with dyskinesias [2,31].

As a result of rapid intestinal absorption and metabolic elimination, plasma levodopa concentrations can fluctuate widely [32]. Early in the course of illness, there is no clear-cut relationship between plasma levodopa profile and antiparkinsonian effect [33]. With the progression of the disease, a correlation between levodopa plasma concentration and clinical effect emerges [34]. In more advanced stages of Parkinson's disease the clinical response mirrors the rapid rise and fall in plasma levodopa concentrations after each dose (the 'wearing-off' phenomena). At this point, even small changes in levodopa disposition can greatly affect the therapeutic response. Long-term levodopa administration results in an increased levodopa plasma bioavailability in patients with Parkinson's disease. This may result from deteriorated peripheral activity of levodopa metabolizing enzymes or an increasing enteric dysfunction with subsequent better duodenal levodopa absorption or both [35,36]. The pharmacokinetic optimization of levodopa dosage becomes essential to obtain reproducible plasma profiles and matched therapeutic responses [15,37].

Since then, several techniques such as continuous levodopa infusion or long-acting levodopa combinations have been proved to overcome complications with levodopa therapy.

In this review, the studies carried out evaluating levodopa and dietary factors' interaction will be included.

2. Levodopa–fiber interaction

2.1 In rabbits with normal gastrointestinal function

An experimental study was carried out in rabbits to evaluate the influence of *Plantago ovata* husk on the pharmacokinetics of levodopa after a single administration of the drug [38]. Fiber was given immediately before levodopa administration at two different doses: 100 and 400 mg/kg.

The results of this study indicate (Table 1) that after the administration of the low dose of *P. ovata* husk, the mean AUC values calculated were slightly lower than when levodopa was administered without fiber. However, when the fiber was administered at the dose of 400 mg/kg, the mean AUC value was higher than in the other two groups, although the differences were not significant. The fraction of dose absorbed is 40.26% when levodopa is administered alone, 37.15 when 100 mg/kg of *P. ovata* husk is given and 53.16 when the dose of fiber is 400 mg/kg.

Table 1. Pharmacokinetic parameters obtained by non-compartmental analysis in rabbits after administration of levodopa 20 mg/kg p.o. alone and with 100 or 400 mg/kg *Plantago ovata* husk.

Parameters	Levodopa alone	Levodopa and 100 mg/kg *P. ovata* husk	Levodopa and 400 mg/kg *P. ovata* husk
λ (min^{-1})	0.0072	0.0057*	0.0133*
AUC (μg/min/ml)	47.1	43.4	62.2
C_{max} (μg/ml)	1.43	1.04	1.46
t_{max} (min)	10.0	20.0	20.0
MRT (min)	29.7	49.5*	42.9*
F (%)	40.3	37.2	53.2

*Significant differences with levodopa alone group (Duncan test, $p \leq 0.05$).
MRT: Mean residence time.

The value of C_{max} also diminished after the administration of the low dose of *P. ovata* husk, but it was similar when levodopa was administered alone and with 400 mg/kg fiber.

The most important fact found in this study is that the amount of levodopa available from a certain time on is always higher in the presence of fiber. In this way, after its administration in the presence of 100 mg/kg fiber, from 60 min on it was 2 times higher than when it was administered alone and when *P. ovata* husk was administered at the dose of 400 mg/kg, the amount of drug available from 20 min on after administration increased 67%.

A further study using the same doses of the drugs was carried out to evaluate the influence of fiber co-administration on levodopa pharmacokinetics, but when levodopa was used combined with carbidopa, as is usually done in daily treatment [39]. The presence of 100 mg/kg *P. ovata* husk diminished the values of AUC and C_{max} for levodopa (29.7 and 28.1%, respectively) in relation to the values obtained when levodopa and carbidopa were administered without fiber (Table 2). If the dose of fiber administered was 400 mg/kg, the decrease was smaller: 20.4% for AUC and 24.6% for C_{max}.

As in the previous study [38], the amount of levodopa available from certain time on was higher when fiber was administered. In this way, the amount of levodopa was 79.2% higher in the presence of 100 mg/kg fiber from 210 min on and 20.3% higher from 150 min on when the dose of fiber was 400 mg/kg than when levodopa and carbidopa were administered without *P. ovata* husk.

In these two studies [38,39] the results indicate that the administration of *P. ovata* husk conduced to an improvement of several pharmacokinetic parameters of levodopa: higher final concentrations of levodopa, a longer plasma half-life and lower C_{max} values, although the AUC values diminished. This could indicate that *P. ovata* husk has a similar mechanism of action as carbidopa (inhibition of l-amino acid aromatic decarboxylase) and would need a period of time to stabilize its action.

Taking into account the results obtained in a single administration [38,39], the same authors evaluated in rabbits the influence of treatment duration with *P. ovata* husk/levodopa/carbidopa (7 or 14 days) on the bioavailability and other pharmacokinetic parameters of levodopa [40].

When levodopa and carbidopa were administered with 100 or 400 mg/kg of *P. ovata* husk, the mean AUC and C_{max} values increased significantly from days 1 to 7 and from days 1 to 14, the values being very similar on days 7 and 14 (Table 2).

After 7 or 14 days of treatment, the AUC was higher (12.7%) on administering 400 mg/kg fiber than when 100 mg/kg fiber was used, whereas C_{max} was almost the same.

The values obtained for C_{min} in the groups studied increased progressively with the duration of treatment. It was observed that with a longer duration of treatment, there was an improvement in the extent of levodopa absorbed, resulting in higher final concentrations. These values were stabilized between days 7 and 9 of treatment.

2.2 In constipation

One of the major problems in the daily life of patients with Parkinson's disease is gastrointestinal dysfunction, especially constipation. It is estimated that ~ 60 – 80% of Parkinson's disease patients suffer from constipation. Several studies have proved that constipation appears – 10 – 20 years prior to motor symptoms [41-44]. More recently, Abbott *et al.* [45] have found from a large scale prospective study that lower frequency bowel movements predict the future risk of Parkinson's disease.

Constipation is included among the non-motor symptoms, which are often poorly recognized and inadequately treated in contrast with the dopaminergic symptoms of the disease, for which treatment is available. These non-dopaminergic and non-motor symptoms are sometimes present before diagnosis and almost inevitably emerge with disease progression. Indeed, non-motor symptoms dominate the clinical picture of advanced Parkinson's disease and contribute to severe disability, impaired quality of life and shortened life expectancy [44].

As constipation and slow gastric emptying are frequent in patients with Parkinson's disease [46-52], different approaches to its treatment have been investigated. Drugs that block

Table 2. Pharmacokinetic parameters obtained by non-compartmental analysis in rabbits after administration of levodopa/carbidopa (LD/CD) 20:5 mg/kg p.o. alone and with 100 or 400 mg/kg *Plantago ovata* husk.

Parameters	LD/CD	Levodopa and 100 mg/kg *P. ovata* husk					Levodopa and 400 mg/kg *P. ovata* husk				
		Normal rabbits			Constipated rabbits		Normal rabbits			Constipated rabbits	
		Single	7 Days	14 Days	7 Days	14 Days	Single	7 Days	14 Days	7 Days	14 Days
λ (min^{-1})	0.0139	0.0083	0.0079	0.0098	0.0091	0.0071	0.0123	0.0134	0.0115	0.0079	0.0084
AUC (µg/min/ml)	155	109	141.3*	148.8*	171.67*	174.13*	129	159.2*	167.2*	171.33*	182.44*
C_{max} (µg/ml)	2.74	1.97	2.21	2.30	2.03	1.99	2.07	2.25	2.30	1.92	1.99
t_{max} (min)	20.0	20.0	20.0	20.0	20.0	20.00	20.0	20.0	20.0	20.0	20.0
MRT (min)	57.6	70.7	74.6	72.0	102.7*	119.1*	63.5	78.9	83.2	120.5*	118.7*

*Significant differences with levodopa alone group (Duncan test, $p \leq 0.05$).
MRT: Mean residence time.

dopamine receptors, presumably via an effect on gastric dopamine receptors, accelerate gastric emptying [53] and may improve levodopa absorption. Metoclopramide hydrochloride speeds up gastric emptying but is contraindicated in Parkinson's disease because it readily gains access to the CNS and blocks striatal dopamine receptors, thus exacerbating parkinsonism. Results with domperidone are contradictory. Domperidone blocks dopamine receptors but does not cross the blood–brain barrier, and it has been reported that it can be used safely in Parkinson's disease and improves both gastric emptying, measured objectively, and symptoms of gastroparesis in patients with Parkinson's disease [54]. However, other authors [55] have indicated that it can exacerbate parkinsonism.

Cisapride acts as a prokinetic agent by stimulating acetylcholine release from myenteric cholinergic neurons [56]. This drug can also increase plasma concentrations of levodopa [57] and reduce levodopa dose failures [58] in patients with Parkinson's disease, but concerns about potential cardiotoxicity have led to a ban on or severe restriction of the use of cisapride in many countries.

Another approach would be the use of fiber. Fiber therapy could be employed to reduce the symptoms of gastrointestinal motility disorders, because it regulates stool transit in the small as well as in the large intestines [59,60]. Increased intake of water becomes essential during fiber therapy and it also represents a good treatment option for constipation. However, concomitant administration of fiber can modify the absorption kinetics of levodopa and, consequently, the plasmatic concentrations. Pharmacokinetic drug interactions have been the subject of numerous studies, but few of them have been carried out with dietary fiber, the results obtained being variable.

Ashraf *et al.* [43] indicated that among patients with Parkinson's disease who had confirmed constipation, *P. ovata* husk increased stool frequency and weight but did not alter colonic transit or anorectal function. They concluded that *P. ovata* husk produces both subjective and objective improvements in constipation related to Parkinson's disease.

A possible problem is that fiber administration could delay gastric emptying and, consequently, delay levodopa absorption from the gastrointestinal tract and increase its presystemic elimination [61]. The effect of fiber on gastric emptying is controversial. Benini *et al.* [62] stated that fiber naturally present in food delays gastric emptying of a solid meal. When using guar gum, another hydrosoluble fiber, gastric emptying [63] and intestinal transit were delayed [64]. According to Bergmann *et al.* [65], the intake of 10.8 g of psyllium significantly delayed gastric emptying 3 h after a meal.

In 1992, Astarloa *et al.* [66] found that the consumption of a highly insoluble fiber (bran of wheat and pectin) diet with levodopa for 2 months caused a 71% increase in levodopa bioavailability via an increase in gastrointestinal motility in patients with Parkinson's disease who also had severe constipation. These authors also described an improvement in patients' motor function (coordination) and constipation.

Other authors [67] evaluated the effects of the hydrosoluble fiber *P. ovata* husk on levodopa pharmacokinetics (administered with carbidopa) in rabbits while administering biperiden to slow gastrointestinal motility. The treatment lasted for two different periods of time (7 and 14 days) to verify the stabilization of levodopa concentrations and the gastrointestinal fiber effect. *Plantago ovata* husk was administered at two different doses of 100 and 400 mg/kg to allow evaluation of whether pharmacokinetic modifications are fiber-dose dependent (Table 2).

In this study it was found that constipation reduced the amount of levodopa absorbed, with a decrease in the values of AUC and C_{max}. After several days of constipation, C_{max} remained low and AUC values increased near to those found in normal rabbits. The presence of 100 or 400 mg/kg fiber in the treatment caused an important increase in the values of AUC and C_{max}, with no significant differences in the values of the pharmacokinetic parameters determined on days 7 or 14.

2.3 Mechanism of levodopa–fiber interaction

One of the possible mechanisms that would explain the interaction between fiber and drugs is a modification in gastric emptying. This mechanism would be important for levodopa

due to the stomach having a very limited capacity to absorb this drug, but can decarboxylate it [15].

Several soluble dietary fibers such as guar gum or pectin have been shown to delay the gastric emptying of liquids and solids, probably due to an increase in meal viscosity [68]. Nevertheless, other authors did not find this action: Bianchi and Capurso [69] demonstrated that the addition of different dietary fibers (guar gum and ispaghula) to a solid meal did not influence gastric emptying. Frost *et al.* [70] probed that psyllium-enriched pasta had no significant effect on gastric emptying and Rigaud *et al.* [71] concluded that psyllium did not slow down the gastric emptying of hydrosoluble nutrients, but increased the time allowed for intestinal absorption.

Some changes in the pharmacokinetic parameters of levodopa after its administration with *P. ovata* husk [38-40] could be due to a delay in the gastric emptying of the drug that would lead to a greater degradation of levodopa in the stomach. However, other authors [71-73] think that these changes principally occur because the fiber forms a highly viscous solution, trapping levodopa inside it, and, therefore, there is a decrease in drug absorption in the intestine and consequently lower values for C_{max} are obtained.

Another mechanism, the modification in the presystemic metabolism of levodopa, which is different from those previously pointed out, could also participate in the interaction between levodopa and fiber. This fact will lead to an increase in the extent of levodopa absorbed.

Following oral administration, levodopa is highly metabolized to dopamine by the enzyme aromatic amino acid decarboxylase in the gut [74]. Fiber, or the products derived from its partial hydrolysis in the stomach, could diminish its presystemic metabolism since certain time on, resulting in higher concentrations of levodopa since that moment.

It has been found that dietary fiber, and hydrosoluble fiber in particular, can modify the intestinal enzymatic activity, both the gut wall enzymes [75] as well as those of the intestinal content [75,76]. Results obtained by several authors regarding the impact of *P. ovata* husk on the enzyme activity are contradictory. Leng-Peschlow [77] concluded that this fiber had no effect (pepsin, trypsin, alpha-amilase) or a stimulating action (chymotrypsin, lipase, lactase). Nevertheless, Isaksson *et al.* [76] found that *P. ovata* husk affected the lipase activity, which was moderately inhibited; Hansen [78] established that this fiber led to an inhibition of the activity of proteolytic pancreatic enzymes *in vitro*; and Leng-Peschlow [77] indicated that it reduced β-glucuronidase activity in rats.

On the other hand, Hansen [78] indicated that the fiber effect on proteolytic enzyme activity was proportional to fiber concentration and inversely related to enzyme level.

Another aspect that can participate in the interaction with the fiber is a modification in the paracellular absorption of levodopa across the gut wall, avoiding its possible degradation by the enzymes located inside the cells of the gut wall.

The presence of fiber could increase the paracellular transport of levodopa, which would contribute to a higher absorption of the unaltered drug. Lennernäs *et al.* [79] proposed that levodopa, a small and hydrophilic molecule, can be absorbed by the paracellular route. However, further studies [80] concluded that the variability in the absorption of levodopa in Parkinson's disease cannot be explained by differences in transmucosal water flux in the human small intestine.

3. Effects of proteins on levodopa pharmacokinetics

Several studies have been conducted to evaluate the effect of dietary protein on the clinical response to levodopa due to the transport of levodopa through the L-neutral amino acid transport system [81-90]. The results of these studies showed that the clinical effect of levodopa was reduced by a daily diet containing protein in excess of 1.6 g/kg or a single protein load of ~ 28 g [81-83].

The pharmacokinetics of levodopa after a single oral dose was investigated in eight healthy young volunteers in the fasted state and following isocaloric meals containing either 10.5 or 30.5 g of protein [84]. In this study there was no evidence that consumption of a meal containing 30.5 g of protein impaired either the rate or the extent of absorption of levodopa. Therefore, the reported beneficial effects of a low protein diet in the treatment of patients with Parkinson's disease probably result from reduced competition for levodopa transport across the blood–brain barrier.

The results obtained in patients with Parkinson's disease indicate that aromatic amino acids interfere in the absorption and brain penetration of levodopa, and lowering protein intake improves the quality of the response [85-89]. Other authors [91] measured the brain uptake of L-[18F] fluorodopa by positron emission tomography in a healthy male volunteer both under fasting conditions and during intravenous amino acid loading and they found a significant reduction of tracer uptake into the brain with amino acid loading. It was also shown that since a rich protein diet has been known to impair the clinical effect of levodopa, this protein effect is probably not due to competitive intestinal absorption of levodopa [90]. A study using positron emission tomography showed the decreased effect appeared to be correlated with a decrease in the uptake of levodopa into the brain probably due to competition from the increased plasma amino acid concentrations [91].

4. Effects of other dietary factors on levodopa pharmacokinetics

4.1 Juices

A study carried out in rats [92] evaluated the influence of banana juice on levodopa bioavailability. The authors found that when levodopa preparation was orally administered with banana juice made by mixing fresh banana and water, there was a decrease in AUC and C_{max}. However, if a

commercial beverage containing 10% banana juice was used, there were no modifications in these parameters.

4.2 Herbal medicines

A reduction in levodopa oral bioavailability was also found after its administration with several over-the-counter (OTC) kampo medicines for stomach: Takeda Kampo Ichoyaku K-matsu (preparation A), Taisho Kampo Ichoyaku (preparation B) or Kanebo Kampo Ichoyaku H (preparation C), which are OTC herbal medicines for upset stomach [93]. The plasma levodopa concentration–time curves were shifted downwards and the AUC for levodopa was significantly lowered.

On the other hand, concomitant administration of the levodopa preparation with Takeda Kampo Ichoyaku A-matsu (preparation D) did not alter any of the pharmacokinetic parameters for levodopa [93]. According to the package inserts for the OTC kampo medicines, preparations A, B and C, but not D, contain metallic additives, such as aluminum silicate and magnesium stearate. From these results, it was concluded that metallic additives may play an essential role in generating the drug interaction between levodopa preparation and OTC kampo medicine for upset stomach.

4.3 The time of ingestion of a meal

Several authors studied the effect of the time of ingestion of a meal on the pharmacokinetics and pharmacodynamics of levodopa [94,95]. The influence of meal ingestion time on rate and extent of oral levodopa absorption was evaluated in a group of 17 patients, after administration of their usual second daily dose of levodopa plus carbidopa or benserazide [94]. Standard meals were consumed by the patients after they had fasted 15 – 17 h, on one occasion 30 min before ingestion of the levodopa 'study dose' and at another time, 2 h after ingestion of the same dose. The results of this study indicated that the time to peak plasma levodopa concentration increased threefold when levodopa was administered after meals and the area under the 6-h plasma concentration–time curve for levodopa was decreased in 10 subjects, unchanged in 3 and higher in 4 after ingestion of meals, the latter finding probably resulting from an erratic absorption even at fasting. On the whole, levodopa absorption proved significantly lower, 15% on an average. Similarly, peak plasma levodopa concentrations were lower in 12 patients, unchanged in 2 and higher in 3, with an overall significant decrease of 30% on the average.

A further study [95] assessed the effect of the time of ingestion of a meal on the pharmacokinetics and pharmacodynamics of a levodopa/carbidopa controlled-release formulation in parkinsonian patients on chronic levodopa therapy. Controlled release levodopa intake after meals resulted in a significant delay in drug absorption, with an almost twofold increase in time of initial appearance of levodopa in plasma and time to peak plasma concentration. Peak plasma drug concentrations were not significantly different in the two experimental conditions; the area under the 6-h plasma concentration–time curve showed an average reduction of 24% in the fed condition, partly reflecting the incomplete assessment of levodopa absorption. These authors concluded that time of meal ingestion is an important determinant of levodopa disposition, even from controlled-release levodopa preparations in parkinsonian patients and that the results of the trial, from a clinical point of view, could explain some of the delayed, curtailed and even lacking responses that often complicate afternoon motor performances in patients at the more advanced stages of the disease.

4.4 Fat

In an open-label, two-way cross-over study, the effects of a high-fat breakfast, administered 30 min before drug administration, on the pharmacokinetics of levodopa was evaluated in 19 healthy volunteers who had fasted overnight [96]. It was found that this food decreases the rate of levodopa absorption, but had no effect on the systemic exposure to levodopa due to the parameter C_{max} of levodopa being significantly lower and t_{max} longer under postprandial conditions than under fasting conditions with no variations in AUC.

4.5 Ascorbic acid

Levodopa therapy in combination with ascorbic acid may be one of the strategies for Parkinson's disease treatment. Several reports have indicated that ascorbic acid can reduce levodopa dosage without losing its effectiveness. In this way, ascorbic acid can improve levodopa absorption in elderly patients with poor levodopa bioavailability [97] causing significant increases in AUC and C_{max}. Other authors [98] concluded that ascorbic acid was a useful therapy in some parkinsonian patients whose motor complications are not managed with conventional drug treatment.

5. Expert opinion

Levodopa was introduced as an antiparkinsonian oral agent >40 years ago and, since then, it is the most efficacious symptomatic treatment for Parkinson's disease, able to restore dopaminergic striatal stimulation, thus reducing patients' disability and increasing life expectancy. However, the clinical benefit of levodopa tends to deteriorate after the first years of treatment and patients suffer motor fluctuations and dyskinesias, with an incidence of ~ 10%/year acknowledged, which may cause difficulties in the management of the disease. In the initial phase of the disease we can observe the long duration response, which allows a prolonged benefit after a single dose of levodopa, whereas in the advanced phase of the disease, this response decreases and the short duration response becomes evident, generating the fluctuations of the clinical response.

Taking this fact into account, understanding the pharmacokinetic and pharmacodynamic features of the drug is essential for the clinician when prescribing levodopa products in order to maximize its therapeutic effects. It is also very important

for the identification of the factors that can alter levodopa pharmacokinetics. Several reviews of the pharmacokinetics and pharmacodynamics of levodopa have been carried out, many of them in the last years [99-104].

As an amino acid precursor of the neurotransmitter dopamine, levodopa has many unique pharmacokinetic and pharmacodynamic properties that differentiate it from the small, lipophilic drugs that are generally used for treating CNS disorders.

The results of pharmacokinetic and pharmacodynamic studies demonstrate that the effectiveness of levodopa is greatly influenced by its pharmacokinetic characteristics. It appears that once patients are turned 'on', the duration of levodopa effects may be correlated with plasma concentration of levodopa.

Levodopa pharmacokinetics is quite complex, along its passage across gastrointestinal tract, until duodenal absorption. Levodopa absorption may become difficult because of competitive mechanisms with some diet compounds, or because of interference with some concomitant medications. The problems related to 'long-term levodopa syndrome' [105] have been at the center of a number of debates around the delayed versus anticipated start of therapy. It is also not clear what mode of administration of levodopa is best or what the best strategies to optimize the treatment are, maintaining clinical benefits as long as possible and postponing the possible occurrence of motor complications as late as possible.

Strategies to obtain these benefits have been at the heart of scientific debates in recent years. Some of them demonstrated inefficacy, such as the use of prolonged-release levodopa formulations, which substantially do not increase bioavailability of the drug, but only determine a delayed release of the substance, which is often unpredictable. Recently, it has been proved that adjunction of the COMT inhibitor entacapone to levodopa/carbidopa improves motor symptoms in patients with Parkinson's disease, increasing the amount of levodopa available in the brain [26,29,30].

Other strategies aimed at interacting with pharmacokinetics, for instance, increasing the absorption of levodopa through liquid solutions, proved effective only on specific problems, whereas some other strategies such as intraduodenal infusion have been introduced [106].

During a treatment with levodopa, it is very important to consider the possible interactions with dietary factors. Some dietary components, such as amino acids, can lower levodopa bioavailability, whereas others, such as fiber or ascorbic acid, can improve it, representing possibilities to increase levodopa disposition.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Olanow CW. The pathogenesis of cell death in Parkinson's disease. Mov Disord 2007;22(Suppl 17):S335-42
2. Olanow CW, Obeso JA, Stocchi F. Continuous dopamine-receptor treatment of Parkinson's disease: scientific rationale and clinical implications. Lancet Neurol 2006;5:677-87
3. Goldberg AL. Protein degradation and protection against misfolded or damaged proteins. Nature 2003;426:895-9
4. Cotzias GC, Papavasiliou PS, Gellene R. L-dopa in Parkinson's syndrome. N Engl J Med 1969a;281:272
5. Cotzias GC, Papavasiliou PS, Gellene R. Modification of parkinsonism–chronic treatment with L-dopa. N Engl J Med 1969b;280:337-45
6. Leiva C. Más de 20 años de Madopar. Rev Neurol 1997;25:1957-63
7. Cotzias GC, van Woert MH, Schiffer L. Aromatic amino acids and modification of parkinsonism. N Eng J Med 1967;276:374-91
8. Rajput AH, Uitti RJ, Offord KP. Timely levodopa (LD) administration prolongs survival in Parkinson's disease. Parkinsonism Relat Disord 1997;3:159-65
9. LeWitt PA, Taylor DC. Protection against Parkinson's disease progression: clinical experience. Neurotherapeutics 2008a;5:210-25
10. LeWitt PA. Levodopa for the treatment of Parkinson's disease. N Engl J Med 2008b;359:2468-76
• **The reference selected is a more recent and complete one that can provide actual and important information.**
11. Linazasoro G. Pathophysiology of motor complications in Parkinson disease: postsynaptic mechanisms are crucial. Arch Neurol 2007;64:137-40
12. Chan PL, Nutt JG, Holford NH. Levodopa slows progression of Parkinson's disease: external validation by clinical trial simulation. Pharm Res 2007;24:791-802
13. Ahlskog JE, Muenter MD. Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001;16:448-58
14. Hely MA, Morris JG, Reid WG, Trafficante R. Sidney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years. Mov Disord 2005;20:190-9
15. Rivera-Calimlim L, Morgan JP, Dujovne CA, et al. L-dopa absorption and metabolism by the human stomach. J Clin Invest 1970a;49:79a
• **The reference selected is a more recent and complete one that can provide actual and important information.**
16. Rivera-Calimlim L, Dujovne CA, Morgan JP, et al. L-dopa treatment failure: explanation and correction. Br Med J 1970b;10:93-4
17. Wade DN, Mearrick PT, Birkett DJ, Morris J. Variability of L-dopa absorption in man. Aust NZ J Med 1974;4:138-43
18. Bredberg E, Tedroff J, Aquilonius SM, Paalzow L. Pharmacokinetics and effects of levodopa in advanced Parkinson's disease. Eur J Clin Pharmacol 1990;39:385-9

19. Contin M, Riva R, Martinelli P, et al. Pharmacodynamic modeling of oral levodopa: clinical application in Parkinson's disease. Neurology 1993;43:367-71

20. Grahnen A, Eckernas SA, Collin C, et al. Comparative multiple-dose pharmacokinetics of controlled-release levodopa products. Eur Neurol 1992;32:343-8

21. Pinder RM, Brogden RN, Sawyer PR, et al. Levodopa and decarboxylase inhibitors: a review of their clinical pharmacology and use in the treatment of parkinsonism. Drugs 1976;11:329-77

22. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. Clin Pharmacokinet 1987;13:141-78

23. Wilding IR, Hardy JG, Davis SS, et al. Characterisation of the in vivo behaviour of a controlled-release formulation of levodopa (Sinemet CR). Clin Neuropharmacol 1991;14:305-21

24. Jonkers N, Sarre S, Ebinger G, Michotte Y. Benserazide decreases central AADC activity, extracellular dopamine levels and levodopa decarboxylation in striatum. J Neural Transm 2001;108:559-70

25. Müller T. Levodopa/carbidopa and entacapone in the treatment of Parkinson's disease: efficacy, safety and patient preference. Patient Pref Adher 2009;3:1-9

• **The reference selected is a more recent and complete one that can provide actual and important information.**

26. Müller T, Woitalla D, Goetze O, Erdmann C. Entacapone improves absorption of a co-administered salt in patients with Parkinson's disease. Mov Disord 2008;23(10):1458-61

27. Müller T, Erdmann C, Muhlack S, et al. Pharmacokinetic behaviour of levodopa and 3-O-methyldopa after repeat administration of levodopa/carbidopa with and without entacapone in patients with Parkinson's disease. J Neural Transm 2006;113(10):1441-8

28. Müller T, Erdmann C, Muhlack S, et al. Inhibition of catechol-O-methyltransferase contributes to more stable levodopa plasma levels. Mov Disord 2006;21(3):332-6

29. Müller T, Kolf K, Ander L, et al. Comparison of 200 mg retarded release levodopa/carbidopa–with 150 mg levodopa/carbidopa/entacapone application: pharmacokinetics and efficacy in patients with Parkinson's disease. J Neural Transm 2007;114(11):1457-62

30. Müller T, Erdmann C, Bremen D, et al. Impact of gastric emptying on levodopa pharmacokinetics in Parkinson's disease patients. Clin Neuropharmacol 2006;29(2):61-7

31. Shoulson I, Glaubiger GA, Chase TN. On-off response. Clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. Neurology 1975;25:1144-8

32. Kempster PA, Frankel JP, Bovingdon M, et al. Levodopa peripheral pharmacokinetics and duration of motor response in Parkinson's disease. J Neurol Neurosurg Psychiatry 1989;52:718-23

33. Deleu D, Sarre S, Ebinger G, Michotte Y. In vivo pharmacokinetics of levodopa and 3-O-methyldopa in muscle. A microdialysis study. Naunyn Schmiedebergs Arch Pharmacol 1991;344:514-9

34. Castro A, Valldeoriola F, Linazasoro G, et al. Optimizacion del uso de la levodopa en la enfermedad de Parkinson: papel de la combinacion levodopa-carbidopa-entacapona. Neurologia 2005;20:180-8

35. Woitalla D, Goetze O, Kim JI, et al. Levodopa availability improves with progression of Parkinson's disease. J Neurol 2006;253(9):1221-6

36. Muhlack S, Woitalla D, Welnic J, et al. Chronic levodopa intake increases levodopa plasma bioavailability in patients with Parkinson's disease. Neurosci Lett 2004;363:284-7

37. Van Laar T. Levodopa-induced response fluctuations in patients with Parkinson's disease: strategies for management. CNS Drugs 2003;17:475-89

38. Garcia JJ, Fernandez N, Carriedo D, et al. Hydrosoluble fiber (Plantago ovata husk) and levodopa I: experimental study of the pharmacokinetic interaction. Eur Neuropsychopharmacol 2005;15:497-503

39. Fernandez N, Carriedo D, Sierra M, et al. Hydrosoluble fiber (Plantago ovata husk) and levodopa II: experimental study of the pharmacokinetic interaction in the presence of carbidopa. Eur Neuropsychopharmcol 2005;15:505-9

40. Diez MJ, Garcia JJ, Prieto C, et al. The hydrosoluble fiber Plantago ovata husk improves levodopa (with carbidopa) bioavailability after repeated administration. J Neurol Sci 2008;271:15-20

• **The reference selected is a more recent and complete one that can provide actual and important information.**

41. Özge A, Bugdayci R, Togrol E, Saracoglu M. The relation of gastrointestinal symptoms to duration of levodopa treatment and severity of Parkinson's disease. J Appl Res 2003;3:349-55

42. Singaran C, Ashraf W, Gaumnitz EA, et al. Dopaminergic defect of enteric nervous system in Parkinson's disease patients with chronic constipation. Lancet 1995;346:861-4

43. Ashraf W, Pfeiffer RF, Park F, et al. Constipation in Parkinson's disease: objetive assessment and response to psyllium. Mov Disord 1997;12: 946-51

44. Jost WH, Schimrigk K. Constipation in Parkinson's disease. Klin Wochenschr 1991;69:906-9

45. Abbott RD, Ross GW, White LR, et al. Environmental, life-style, and physical precursors of clinical Parkinson's disease: recent findings from the Honolulu-Asia Aging Study. J Neurol 2003;3:III30-9

46. Byrne KG, Pfeiffer R, Quigley EMM. Gastrointestinal dysfunction in Parkinson's disease: a report of clinical experience at a single center. J Clin Gastroenterol 1994;19:11-6

47. Edwards LE, Pfeiffer RF, Quigley EMM. Gastrointestinal dysfunction in Parkinson's disease: frequency and pathophysiology. Neurology 1992;42:726-32

48. Edwards LL, Pfeifer RF, Quigley EMM, et al. Gastrointestinal symptoms in Parkinson's disease. Mov Disord 1991;6:151-6

49. Hardoff R, Saula M, Tamir A, et al. Gastric emptying time and gastric motility in patients with Parkinson's disease. Mov Disord 2001;16:1041-7

50. Müller-Lissner SA, Kamm MA, Scarpignato C, Wald A. Myths and

misconceptions about chronic constipation. Am J Gastroenterol 2004;100:232-44

51. Quigley EMM. Gastrointestinal dysfunction in Parkinson's disease. Semin Neurol 1996;16:245-50

52. Koller WC, Rueda MG. Mechanism of action of dopaminergic agents in Parkinson's disease. Neurology 1998;50:S11-4

53. McCallum RW. Review of the current status of prokinetic agents in gastroenterology. Am J Gastroenterol 1985;80:1008-16

54. Soykan I, Sarosiek I, Shifflett J, et al. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. Mov Disord 1997;12:952-7

55. Lesser J, Bateman DN. Domperidone. Br Med J 1985;290:241

56. Wiseman LR, Faulds D. Cisapride: an updated review of its pharmacology and therapeutic efficacy as a prokinetic agent in gastrointestinal motility disorders. Drugs 1994;47:116-52 http://adisonline.com/drugs/pages/issuelist.aspx

57. Neira WD, Sanchez V, Mena MA, de Yebenes JG. The effects of cisapride on plasma L-dopa levels and clinical response in Parkinson's disease. Mov Disord 1995;10:66-70

58. Djaldetti R, Koren M, Ziv I, et al. Effect of cisapride on response fluctuations in Parkinson's disease. Mov Disord 1995;10:81-4

59. Voderholzer WA, Schatke W, Muhldorfer BE, et al. Clinical response to dietary fiber treatment of chronic constipation. Am J Gastroenterol 1997;92(1):95-8

60. Badiali D, Corazziari E, Habib FI, et al. Effect of wheat bran in the treatment of chronic nonorganic constipation. A double-blind controlled trial. Dig Dis Sci 1995;40:349-56

61. Fermaglich J, O'Doherty DS. Effect of gastric motility on levodopa. Dis Nerv Syst 1972;33:624-5

62. Benini L, Castellani G, Brighenti F, et al. Gastric emptying of a solid meal is accelerated by the removal of dietary fiber naturally presented in food. Gut 1995;36:825-30

63. Harju E, Heikkila J, Larmi TK. Effect of guar gum on gastric emptying after gastric resection. J Parenter Enternal Nutr 1984;8:18-20

64. Schonfeld J, Evans DF, Wingate DL. Effect of viscous fiber (guar) on postprandial motor activity in human small bowel. Dig Dis Sci 1997;42:1613-7

65. Bergmann JF, Chassany O, Petit A, et al. Correlation between echographic gastric emptying and appetite. Influence of psyllium. Gut 1992;33:1042-3

66. Astarloa R, Mena MA, Sanchez V, et al. Clinical and pharmacokinetic effects of a diet rich in insoluble fiber on Parkinson disease. Clin Neuropharmacol 1992;15:375-80

67. García JJ, Fernández N, Calle AP, et al. Effects of Plantago ovata husk on levodopa (with carbidopa) bioavailability in rabbits with autonomic gastrointestinal disorders. Drug Metab Dispos 2009;37:1434-42

68. Russell J, Bass P. Canine gastric emptying of fiber meals: influence of meal viscosity and antroduodenal motility. Am J Physiol 1985;249:G662-667

69. Bianchi M, Capurso L. Effects of guar gum ispaghula and microcrystalline cellulose on abdominal symptoms gastric emptying orocaecal transit time and gas production in healthy volunteers. Dig Liver Dis 2002;34:S129-33

70. Frost GS, Brynes AE, Dhillo WS, et al. The effects of fiber enrichment of pasta and fat content on gastric emptying GLP-1 glucose and insulin responses to a meal. Eur J Clin Nutr 2003;57:293-8

71. Rigaud D, Paycha F, Meulemans A, et al. Effect of psyllium on gastric emptying hunger feeling and food intake in normal volunteers: a double blind study. Eur J Clin Nutr 1998;52:239-45

72. Fernández N, Diez MJ, Terán MT, et al. Influence of two commercial fibers in the pharmacokinetics of ethinilestradiol in rabbits. J Pharm Exp Ther 1998;286:870-4

73. García JJ, Fernández N, Diez MJ, et al. Influence of two dietary fibers in the oral bioavailability and other pharmacokinetic parameters of ethinyloestradiol. Contraception 2000;62:253-7

74. Andersson I, Granerus AK, Jagenburg R, Svanborg A. Intestinal decarboxylation of orally administered L-dopa. Influence of pharmacological preparations, dose magnitude, dose sequence and food intake. Acta Med Scand 1975;198:415-20

75. Leng-Peschlow E. Plantago ovata seeds as dietary fibre supplement physiological and metabolic effects in rats. Br J Nutr 1991;66:331-49

76. Isaksson G, Lundquist I, Ihse I. Effect of dietary fiber on pancreatic enzyme activity in vitro. Gastroenterology 1982;82:918-24

77. Leng-Peschlow E. Interference of dietary fibres with gastrointestinal enzymes in vitro. Digestion 1989;44:200-10

78. Hansen WE. Effect of dietary fiber on proteolytic pancreatic enzymes in vitro. Int J Pancreatol 1986;1:341-51

79. Lennernäs H, Nilsson D, Aquilonius SM, et al. The effect of L-leucine on the absorption of levodopa studied by regional jejunal perfusion in man. Br J Clin Pharmacol 1993;35:243-50

80. Nilsson D, Fagerholm U, Lennernas H. The influence of net water absorption on the permeability of antipyrine and levodopa in the human jejunum. Pharm Res 1994;11:1540-7

81. Carter JH, Nutt JG, Woodward WR, et al. Amount and distribution of dietary protein affects clinical response to levodopa in Parkinson's disease. Neurology 1989;39:552-6

82. Mena I, Cotzias GC. Protein intake and treatment of Parkinson's disease with levodopa. N Engl J Med 1975;292:181-4

83. Tsui JK, Ross S, Poulin K, et al. The effect of dietary protein on the efficacy of L-dopa: a double-blind study. Neurology 1989;39:549-52

84. Robertson DR, Higginson I, Macklin BS, et al. The influence of protein containing meals on the pharmacokinetics of levodopa in healthy volunteers. Br J Clin Pharmacol 1991;31:413-7

85. Karstaedt PJ, Pincus JH, Coughlin SS. Standard and controlled-release levodopa/carbidopa in patients with fluctuating Parkinson's disease on a protein redistribution diet. A preliminary report. Arch Neurol 1991;48:402-5

86. Bracco F, Malesani R, Saladini M, Battistin L. Protein redistribution diet and antiparkinsonian response to levodopa. Eur Neurol 1991;31:68-71

87. Sanchís G, Mena MA, Martín del Río R, et al. Effect of a controlled low-protein diet on the pharmacological response to levodopa and on the plasma levels of L-dopa and amino acids in patients with Parkinson's disease. Arch Neurobiol (Madr) 1991;54:296-302

88. Nutt JG, Woodward WR, Hammerstad JP, et al. The "on-off" phenomenon in Parkinson's disease. Relation to levodopa absorption and transport. N Engl J Med 1984;310:483-8

89. Frankel JP, Kempster PA, Bovingdon M, et al. The effects of oral protein on the absorption of intraduodenal levodopa and motor performance. J Neurol Neurosurg Psychiatry 1989;52:1063-7

90. 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(3):137-42

91. Leenders KL, Poewe WH, Palmer AJ, et al. Inhibition of L-[18F] fluorodopa uptake into human brain by amino acids demonstrated by positron emission tomography. Ann Neurol 1986;20(2):258-62

92. Ogo Y, Sunagane N, Ohta T, Uruno T. Banana juice reduces bioavailability of levodopa preparation. Yakugaku Zasshi 2005;125(12):1009-11

93. Sunagane N, Aikawa M, Ohta T, Uruno T. Possibility of interactions between prescription drugs and OTC drugs (2nd report)--interaction between levodopa preparation and OTC Kampo medicines for upset stomach. Yakugaku Zasshi 2006;126(11):1191-6

94. Baruzzi A, Contin M, Riva R, et al. Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. Clin Neuropharmacol 1987;10:527-37

95. Contin M, Riva R, Martinelli P, et al. Effect of meal timing on the kinetic-dynamic profile of levodopa/carbidopa controlled release in parkinsonian patients. Eur J Clin Pharmacol 1998;54:303-8

96. 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

97. Linazasoro G, Gorospe A. Treatment of complicated Parkinson disease with a solution of levodopa-carbidopa and ascorbic acid. Neurologia 1995;10(6):220-3

98. Nagayama H, Hamamoto M, Ueda M, et al. The effect of ascorbic acid on the pharmacokinetics of levodopa in elderly patients with Parkinson disease. Clin Neuropharmacol 2004;27(6):270-3

99. Nutt JG. Pharmacokinetics and pharmacodynamics of levodopa. Mov Disord 2008;23:S580-4

• **The reference selected is a more recent and complete one that can provide actual and important information.**

100. Abbruzzese G. Optimising levodopa therapy. Neurol Sci 2008;29:S377-9

• **The reference selected is a more recent and complete one that can provide actual and important information.**

101. Khor SP, Hsu A. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. Curr Clin Pharmacol 2007;2(3):234-43

• **The reference selected is a more recent and complete one that can provide actual and important information.**

102. Ogawa N. Factors affecting levodopa effects in Parkinson's disease. Acta Med Okayama 2000;54(3):95-101

• **The reference selected is a more recent and complete one that can provide actual and important information.**

103. Marras C, Lang AE. Measuring motor complications in clinical trials for early Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74(2):143-6

104. Zappia M, Nicoletti A, Muñoz-S D, Tapia-Núñez J. Reconsiderations in the treatment of Parkinson's disease with levodopa: some pharmacodynamic evidence. Rev Neurol 2009;49(1):33-40

105. Barbeau A. High-level levodopa therapy in Parkinson's disease: five years later. Trans Am Neurol Assoc 1974;99:160-3

106. Antonini A, Tolosa E. Apomorphine and levodopa infusion therapies for advanced Parkinson's disease: selection criteria and patient management. Exp Rev Neurother 2009;9(6):859-67

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