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Research paper

Effects of food on the pharmacokinetics of levodopa in a dual-release formulation

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Abstract

The objective was to assess the effect of food on the pharmacokinetics of levodopa and 3-*O*-methyldopa after administration of a new levodopa/benserazide formulation with a dual-release drug delivery profile (Madopar® DR). In an open-label, two-way cross-over study, 19 healthy volunteers who had fasted overnight were randomized to receive a single oral dose of levodopa/benserazide (200/50 mg) in the absence or presence of a standardized, high-fat breakfast, administered 30 min before drug administration. The treatment periods (fasting, non-fasting) were preceded by a baseline regimen of levodopa/benserazide (100/25 mg t.i.d. for 6 or 7 days). Blood samples were taken at specific times over a 12-hour period. Plasma concentrations of levodopa and 3-*O*-methyldopa were determined by high-performance liquid chromatography for pharmacokinetic evaluation. The parameter C_{max} of levodopa was significantly lower and t_{max} longer under postprandial conditions than under fasting conditions (mean C_{max} 1.41 vs. 2.09 mg l^{-1}; mean t_{max} 3.1 vs. 1.0 h). With food, the area under the curve (AUC) of levodopa was equivalent to that following an overnight fast. Compared with volunteers who had fasted, food did not alter $t_{1/2}$. Estimates of C_{max}, t_{max} and AUC of 3-*O*-methyldopa under non-fasting conditions were not significantly different from those under fasting conditions. In conclusion, food decreases the rate of levodopa absorption, but had no effect on the systemic exposure to levodopa and the degree of 3-*O*-methyldopa formation. Standardization of levodopa/benserazide administration with respect to meal times is recommended.

Keywords: Levodopa; Pharmacokinetics; Effect of food; Dual release; Parkinson's disease

1. Introduction

Levodopa combined with a peripheral inhibitor of aromatic L-amino acid decarboxylase (benserazide, carbidopa) constitutes the most effective medication in the treatment of Parkinson's disease. The fluctuations in clinical response, experienced in patients with advanced Parkinson's disease are a major clinical problem after some years of levodopa treatment. It has been found that some of these fluctuations (e.g. wearing-off, on-off) in motor performance are partially related to the peripheral pharmacokinetics of levodopa [1–4]). Stabilization of plasma levodopa concentrations by administering sustained-release formulations (Madopar® HBS, Sinemet® CR) can reduce response fluctuations [5–8].

A clinical problem inherent to sustained-release levodopa formulations is a delay in onset of clinical benefit, particularly following the first morning dose [5–10]. The failure to produce a reliable and rapid 'kick-start' in the morning, and occasionally also during the day, was overcome by adding instant-release formulations to the treatment program [5–12].

Recently, a dosage form of Madopar has been developed using the Geomatrix® technology which combines instant- and slow-release with the aim of rapidly attaining effective levodopa concentrations and maintaining these over a major part of the dosing interval. The galenical principal of this dual-release formulation, Madopar DR, which contains levodopa and benserazide in the dose range 4:1 in the form of a breakable three-layer matrix tablet (immediate-release layer, barrier, slow-release layer), is based on a biphasic drug-delivery [13]. The particular release characteristics of Madopar DR resulted in rapid absorption and sustained concentrations of levodopa thereafter [13–15].

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The effect of food on the pharmacokinetics of levodopa was studied previously in healthy volunteers after administration of Madopar DR [15]. Food intake slightly increased the rate, but not the extent of levodopa absorption. The study was conducted in a small sample size of 12 volunteers who were pretreated with high-dose benserazide 50 mg t.i.d. for 6 days. Dose–response data showed that benserazide 50 mg t.i.d. did not completely inhibit extracerebral decarboxylase [16]. Long-term administration of levodopa may decrease gut decarboxylase activity [17,18], which is probably responsible for the higher bioavailability of Madopar HBS at steady state [19] compared with the bioavailability after a single dose [20].

The aim of the present study was to re-assess the effect of food on the steady-state pharmacokinetics of levodopa and its main blood metabolite 3-*O*-methyldopa in a larger number of healthy volunteers who received multiple therapeutic doses of levodopa and benserazide in the form of Madopar DR.

2. Materials and methods

2.1. Study protocol and subjects

The study protocol was approved by the 'Comité Consultatif de Protection des Personnes se prêtant à la Recherche Biomédicale (CCPPRB)', Strasbourg, France, and written informed consent was obtained from the subjects after full explanation of the design and objectives of the study prior to the pre-study examination.

Nineteen healthy volunteers (nine males, ten females) were enrolled in the trial. Their mean (range) age, weight and height were 33 years (25–44 years), 71 kg (47–106 kg) and 169 cm (152–188 cm), respectively. The body mass index was 24 kg/m^2 (20–30 kg/m^2). The subjects were in good health as assessed by a pre-study screen, which included a physical examination, a 12-lead ECG, clinical laboratory tests (serum chemistry, hematology, urinalysis) and measurements of vital signs (heart rate, blood pressure). A screen of common drugs of abuse was negative and the subjects smoked no more than 10 cigarettes per day. For the female volunteers the urine pregnancy test was negative at screening visit, prior to drug administration of each treatment period and at follow-up examination.

2.2. Design and clinical procedure

The study had an open-label, randomized, two-way crossover design.

Subjects received one single tablet of Madopar DR (Roche Pharma (Schweiz) AG, Reinach, Switzerland) containing 200 mg levodopa and 50 mg benserazide in the fasting and fed state. Both treatment periods (fasting, non-fasting) were preceded by a baseline regimen of one-half Madopar DR tablet t.i.d. for 6 or 7 days. The last dose of the baseline treatment was taken 10 h prior to the pre-prandial or post-prandial administration of Madopar DR '250'. Following baseline treatment and an overnight fast of at least 10 h, subjects received one tablet Madopar DR '250' under fasting conditions or 5 min after a standard breakfast. Tablets were taken with cold tap water (200 ml) in semi-supine position. Thereafter, the subjects remained semi-supine for the first 4 h after administration of Madopar DR '250'. Afterwards, they were ambulant, but were in a semi-supine position 10 min before each blood sampling period.

The breakfast consisted of three slices of bread (150 g), 30 g cheese, 60 g marmalade, 30 g butter, 200 ml whole milk, 10 g sugar, 100 ml herbal tea, containing 28 g proteins, 43 g fat, 138 g carbohydrate and supplying 1046 kcal. The meal was completely consumed within 25 min. For all subjects, food intake was forbidden during the first 4 h post-dosing. All subjects received standardized meals, 4 and 12 h after drug administration.

Heart rate and blood pressure were determined in semi-supine position (at least 5 min) before medication and at 1, 2, 3, 4 and 12 h after Madopar DR '250' administration. Blood samples were obtained at the screening visit, prior to dosing of Madopar '250' and at follow-up visit for standard laboratory and hematology testing. At the same time points, urine samples were collected for urinalysis.

All adverse events either reported spontaneously by the subjects or observed by the investigator during the study (up to day 24) were recorded.

2.3. Sample collection for pharmacokinetics and drug analysis

Blood samples of 7 ml were collected into tubes containing EDTA as anticoagulant, and sodium metabisulfite (0.2 ml of a 10% solution) as antioxidant, from an indwelling cannula placed in the forearm of the subject, just before, and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 9 and 12 h after drug administration. Samples were put on crushed ice immediately and centrifuged (2000 × *g* at 4 °C for 10 min) not later than 30 min after collection, and the plasma was separated and stored in polypropylene tubes at −25 °C.

Concentrations of levodopa and 3-*O*-methyldopa in plasma were measured by high-performance liquid chromatography (HPLC). The work-up of samples was carried out by perchloric protein precipitation of 0.5 ml plasma at temperature below 20 °C. Following centrifugation, the clear supernatants were transferred to amber HPLC vials and injected into the HPLC system. The same procedure was applied to samples of unknown concentration, calibrator (CAL) and quality control (QC). Quantification of levodopa and 3-*O*-methyldopa in plasma was performed by an electrochemical detector (ECD) at 550 mV. CAL and QC solutions were prepared in plasma and kept frozen under the same conditions as the study samples. Day-to-day analytical performance was assured by the regular analysis of QC samples.

The standard curves for levodopa and 3-*O*-methyldopa

were linear in the range 25–3000 ng/ml and 50–4000 ng/ml, respectively. The limit of quantification of levodopa and 3-*O*-methyldopa was 25 ng/ml and 50 ng/ml, respectively. As assessed by QC samples, the overall inter-assay precision (CV%) was 3.5% for levodopa and 3.1% for 3-*O*-methyldopa, and the overall inaccuracy was 1% for levodopa and 3% for 3-*O*-methyldopa over the concentration range given by the calibrator standards.

2.4. Pharmacokinetic evaluation

The maximum plasma concentration (C_{max}) and the time of its occurrence (t_{max}) were read directly from the individual plasma concentration-time data. The elimination rate constant (λ_z) of levodopa was calculated by fitting the individual data from the terminal phase of the concentration-time plots to log-linear regression using the method of least squares. The apparent elimination half-life ($t_{1/2}$) was calculated by dividing ln 2 by λ_z. The area under the plasma concentration–time curve (AUC) from time zero to the time of the last measurable concentration point (t_n) was calculated using the linear-trapezoidal rule. Extrapolation to time infinity was determined for levodopa by dividing the last measurable concentration point by λ_z. The relative bioavailability (F_{REL}) was calculated by dividing AUC (non-fasting) by AUC (fasting). The 'metabolic ratio' metabolite versus parent drug (R_{MET}) was calculated by dividing the respective AUC (0–t_n) values.

2.5. Statistics

Means and standard deviations (SD) were calculated for all pharmacokinetic parameters. A multiplicative model was assumed for the primary levodopa and 3-*O*-methyldopa parameters C_{max} and AUC which implies a log-normal distribution. The drug–food interaction was assessed on the basis of bioequivalence criteria using the multiplicative model. Schuirman's two one-sided *t*-tests procedure was used for calculating the 90% confidence interval (CI) using the log-transformed data of each bioequivalence metric [21]. The decision in favor of bioequivalence was based on the inclusion of the shortest 90% CI for the ratio of the geometric means (point-estimate) of the treatments (fed versus fasted) in a pre-defined acceptance range. The ranges set for C_{max} and AUC were 0.70–1.43 and 0.80–1.25, respectively [22]. In addition, sequence effects were studied by analysis of variance (ANOVA) of the log-transformed data.

3. Results

3.1. Safety

No subject was withdrawn from the study for safety reasons. Most of the adverse events (AE) occurred at the early stages of the first treatment period. AE were those classically described for levodopa (nausea, vomiting; headache, dizziness, fatigue). Very few AE were observed during the pharmacokinetic study days, and it is difficult to conclude if the frequency or severity of these AE are related to the fasting or non-fasting state. All AE resolved quickly without sequelae. Slight decreases in blood pressure for up to 4 h after drug intake were observed in nine subjects. In general, the lowest values were observed 1–2 h and 3–4 h in fasting and non-fasting condition, respectively. There was no clear pattern of abnormal laboratory values to suggest a treatment effect.

3.2. Pharmacokinetics

The mean plasma concentration-time profiles of levodopa and 3-*O*-methyldopa after administration of Madopar DR in the fed and fasting state are presented in Fig. 1. The mean (SD) parameter estimates from the plasma concentration-

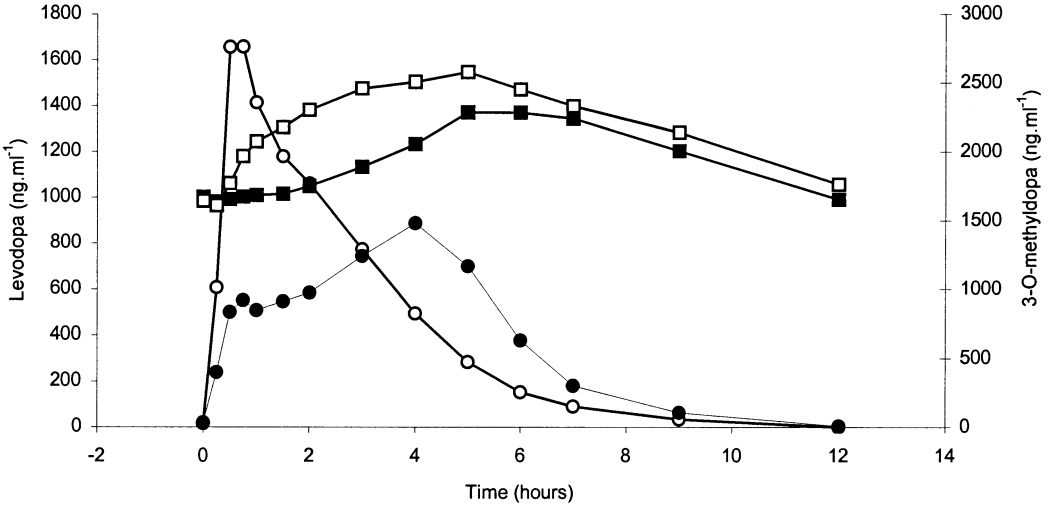

Fig. 1. Plasma concentration-time profiles of levodopa (○, fasting; ●, fed) and 3-*O*-methyldopa (□, fasting; ■, fed) after administration of Madopar DR in the fed and fasting state (arithmetic means, $n = 19$).

Table 1
Pharmacokinetic parameters of levodopa and 3-*O*-methyldopa in 19 healthy volunteers receiving Madopar DR '250' under fasting and non-fasting conditions[a]

	Levodopa		3-*O*-Methyldopa	
	Fasting	Non-fasting	Fasting	Non-fasting
C_{max} (mg l^{-1})	2.09 (0.65)	1.41 (0.59)	2.60 (0.69)	2.34 (0.65)
t_{max} (h)	1.0 (0.7)	3.1 (1.5)	4.7 (1.0)	5.5 (1.3)
$AUC_{0-12\ h}$ (mg h·l^{-1})	4.76 (1.45)	4.30 (1.34)	26.61 (7.02)	23.59 (6.83)
$AUC_{0-\infty}$ (mg h·l^{-1})	4.87 (1.46)	4.41 (1.35)	ND	ND
$t_{1/2}$ (h)	1.6 (0.5)	1.3 (0.2)	ND	ND

[a] Values are means (SD). ND, not determined.

time data for levodopa and its metabolite are summarized in Table 1. Mean C_{max} values for levodopa were lower by one-third when administered after a standard breakfast compared with dosing after an overnight fast. However, in four of 19 subjects higher C_{max} values of levodopa were observed in the presence of food. Mean t_{max} of levodopa was longer by 2 h in the post-prandial state. The extent of systemic availability (AUC) and the elimination half-life of levodopa were similar among treatments.

The pharmacokinetic parameters of 3-*O*-methyldopa did not differ markedly between non-fasting and fasting conditions. The relative bioavailability (fed/fasted) of levodopa and 3-*O*-methyldopa was close to 90% (Table 2). The 'metabolic ratio', expressed as the AUC ratio of metabolite over levodopa, was unaffected by food intake (Table 2). The point estimates and the 90%-confidence intervals of the primary pharmacokinetic parameters are given in Table 2. The statistical evaluation of the pharmacokinetic data showed that equivalence of the regimens (fed/fasted) could be demonstrated for AUC within the range 80–125% for both levodopa and its metabolite. Equivalence between fasting and non-fasting treatment conditions could not be assumed for C_{max} of levodopa within the range 70–143%.

4. Discussion

The objective of the study was the investigation of the effect of food on the pharmacokinetics of levodopa and 3-*O*-methyldopa after oral administration of a new dual-release formulation of levodopa/benserazide (Madopar DR 200/50 mg) in 19 healthy volunteers who received the tablet either on an empty stomach or after a high-fat breakfast. The volunteers received the treatments (fasting, non-fasting) after a baseline treatment of Madopar DR ('125' mg t.i.d. for 6 or 7 days). The pretreatment was conducted in order to better reflect the therapeutic multiple-dose situation in patients who are under chronic administrations of levodopa/benserazide.

Table 2
Relative bioavailability, 'metabolic ratio' and point estimates [90% confidence interval] for C_{max} and AUC[a]

	Levodopa	3-*O*-Methyldopa
F_{REL}	0.91 (0.13)	0.89 (0.13)
R_{MET}		5.73 (1.29) fasting; 5.57 (1.09) fed
C_{max}	0.65 [0.54–0.79]**	0.90 [0.85–0.95]*
$AUC_{0-12\ h}$	0.90 [0.85–0.96]*	0.88 [0.83–0.94]*
$AUC_{0-\infty}$	0.91 [0.86–0.96]*	ND

[a] Values are means (SD) for F_{REL} and R_{MET}, and point estimates [90% CI] for C_{max} and AUC. *Equivalent; **not equivalent. ND, not determined.

The 'lack of food interaction' was handled as an equivalence problem with 'test' as non-fasting and 'reference' as fasting administration.

Absorption of levodopa occurred more slowly when Madopar DR was taken under non-fasting versus fasting conditions. As a result, peak plasma concentration of levodopa was achieved later and was lower in the post-prandial state.

The rate of gastric emptying is a key factor in the absorption of levodopa [18,23]. Factors which retard gastric emptying, such as meals delay delivery of the drug to the intestinal absorption sites, resulting in delayed and reduced peak plasma concentration of levodopa.

Slower rates of levodopa absorption under non-fasting conditions were previously observed for levodopa/benserazide administered in the form of the immediate-release [24] and slow-release [25] formulation, and also with immediate-release levodopa/carbidopa [26].

The food-induced reduction in the maximum plasma concentration of levodopa was not due to increased presystemic metabolism of levodopa to 3-*O*-methyldopa because the degree of catechol-*O*-methylation, as reflected by the truncated metabolic ratio, was not affected. Accordingly, it is most likely that food ingestion reduced the absorption rate of levodopa by delaying gastric emptying. However, it cannot be excluded that benserazide is transiently less active in inhibiting the decarboxylase when given concomitantly with food. It is noteworthy that even at very high doses of benserazide (200 mg t.i.d.) extracerebral decarboxylase is not completely inhibited [16].

In the present study, the systemic exposure to levodopa as reflected by AUC values was not affected in the presence of food. This finding was observed previously for the slow-release formulation Madopar HBS [25].

The present finding of the reduced absorption rate of levodopa in the fed state is not in accordance with a previous study of Madopar DR conducted in only 12 healthy volunteers [15]. In these subjects the absorption of levodopa was enhanced when Madopar DR was administered after a standard breakfast of almost identical composition. The discrepant results may be explained by multiple peaks in the plasma profile of levodopa commonly observed after oral dosing [18,24,27,28]. In the present study, multiple peaks were observed, even with fasting and under standardized conditions, in four of 19 subjects whereas in the previous study five of 12 subjects had multiple peaks. Multiple plasma peaks of oral levodopa were attributed to erratic gastric emptying [27] explained by an episodic delay in gastric emptying produced by levodopa [29–31]. In the case of multiple peaks a clear and accurate estimation of the maximum levodopa concentration is difficult or impossible. In addition to multiple peaks, the small number of subjects coupled with the large variance in absorption parameters may have precluded an accurate estimation of the absorption rate in the previous study [15].

Another explanation may result from the different study designs used in the present and the previous study [15]. In the latter study subjects were pretreated with benserazide alone, whereas in the present study they were pretreated with both levodopa and benserazide. Levodopa itself inhibits gastric emptying and thus influences its own absorption [29,32,33]. The slower postprandial rate of levodopa observed in the present study may be due to the prolonged inhibition of gastric emptying as a consequence of the baseline treatment with levodopa/benserazide.

The present findings suggest that Madopar DR should always be administered in a constant temporal relationship to food in order to lessen variability within the same individual in terms of absorption rate and, possibly, therapeutic efficacy.

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