Inhibition of L-Phenylalanine Absorption by L-DOPA in Patients with Parkinsonism[1] (35700)

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The use of large doses of L-3, 4-dihydroxyphenylalanine (L-DOPA) in the treatment of parkinsonism was proposed by Cotzias *et al.* (1). L-DOPA has to be given in doses of 2–6 g daily (1, 2). Intake of L-DOPA might interfere with the intestinal absorption of other amino acids. The intestinal amino acid absorption is an active process and there are probably different transport systems. Structurally related amino acids are absorbed by the same mechanism (3). It has been shown that L-3-(3, 4-dihydroxyphenyl)-2-methylalanine (Aldomet) inhibits the absorption of several amino acids including L-phenylalanine in rat intestine (4). It is therefore likely that L-DOPA, when given with food, influences the amino acid absorption, especially the absorption of tyrosine and phenylalanine. The aim of the present investigation was to study the absorption of L-phenylalanine in parkinsonian patients before and during L-DOPA treatment.

Material. The study included 9 parkinsonian patients, 5 men and 4 women. The age ranged from 51 to 77 years (mean 63 years) and the body weight from 50 to 69 kg (mean 59 kg). The patients were studied before and after 4–8 weeks on L-DOPA treatment. The L-DOPA dose was slowly increased (2) during 3–4 weeks to the optimal dose, which was in the range 2.75–4.5 g/day. Each patient was on the same dose of anticholinergic drugs during the investigation period.

Methods. Intravenous L-phenylalanine loading. L-Phenylalanine, 50 mg/kg of body wt (given as a 2.5% solution kindly supplied by AB Astra, Södertälje, Sweden) was injected into a cubital vein in less than 3 min. Blood sampling was performed before the injection and every 3–6 min for the following 150 min. No untoward effects were noticed. For the loading carried out during the L-DOPA treatment for 4–8 weeks, 1 g of L-DOPA was given orally 45 min before the L-phenylalanine injection.

Oral L-phenylalanine loading. The day after the intravenous loading the patient was given 100 mg of L-phenylalanine/kg of body weight. The amino acid was dissolved in 300 ml of coffee. Blood was taken before, 30, 45, 60, 90, 120, and 180 min after the loading. For the loading carried out during L-DOPA treatment for 4–8 weeks, 1 g of L-DOPA was given orally 30 min before L-phenylalanine ingestion to 6 patients. The remaining 3 patients did not receive L-DOPA for the last 12 hours before the loading.

The L-DOPA was given as capsules of 250 mg. Venous blood was drawn from an indwelling catheter into heparinized tubes. The blood samples were immediately centrifuged. The separated plasma was kept frozen until analysis. Phenylalanine and tyrosine were determined spectrofluorometrically (5, 6).

Results. Intravenous L-phenylalanine loading. From the plasma phenylalanine disappearance curve, the rate constant (k_2) of slope 2 (Fig. 1) was calculated in the interval, 50–150 min, after the injection assuming a straight line in a semilogarithmic diagram. From the theoretical concentration at zero time (c_2), the apparent distribution coefficient D/c_2 was calculated, where D is the phenylalanine dose (μmole/kg of body wt). The rate constant (k_1) for the disappearance of phenylalanine during the initial distribu-

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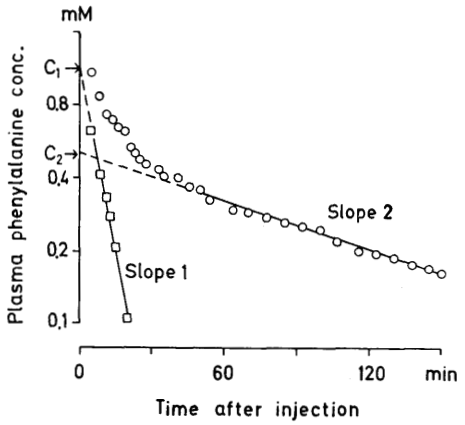

FIG. 1. Plasma phenylalanine disappearance curve (observed value minus fasting value) after intravenous L-phenylalanine loading in patient 3 (○); slope 1 (□) was calculated according to conventional technique.

tion phase (slope 1) was calculated in the interval, 5–25 min, after the injection according to conventional technique (7). The L-DOPA treatment did not result in any significant differences in these parameters (Table I). Patient 4 received no intravenous loading.

Oral loading. Before L-DOPA treatment, oral L-phenylalanine loading gave a rapid increase in the plasma phenylalanine concentration with a maximum within 45 min (Fig. 2) and a mean increase in the tyrosine concentration of 77 μmole/liter with a maximum after 60 min. When 1 g of L-DOPA was given 30 min before the L-phenylalanine dose a less pronounced increase in the plasma phenylalanine concentration was obtained and no definite peak value was reached within 3 hr (patients 1–6, Fig. 2). The increase in the plasma tyrosine concentration was also less pronounced, but the difference was not significant. The 3 patients (7–9), who did not receive L-DOPA in connection with the loading, had almost identical plasma phenyla-

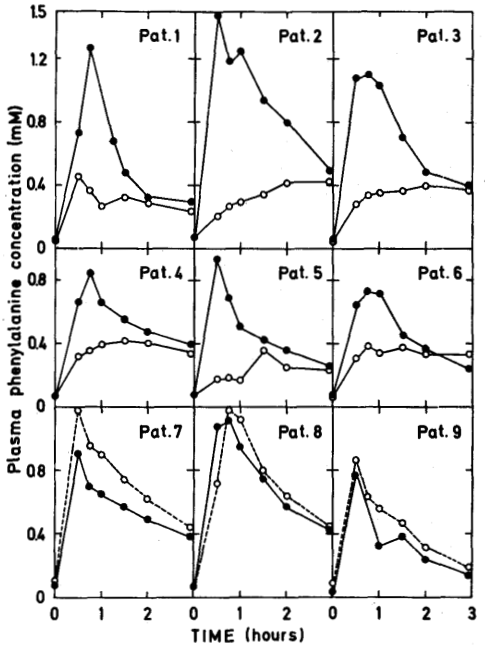

FIG. 2. Plasma phenylalanine concentration after oral L-phenylalanine loading: before (●); and during (○) 4–8 weeks of L-DOPA treatment. Patients 1–6, received L-DOPA 30 min before the L-phenylalanine load. Patients 7–9 did not receive L-DOPA for the last 12 hr.

TABLE I. The Rate Constants (k_1, k_2) and the Distribution Coefficient of Phenylalanine Determined After iv Injection of L-Phenylalanine Before (I) and During L-DOPA Treatment in Parkinsonian Patients.

Subject	Rate constant k_1 (min^{-1})		Rate constant k_2 (min^{-1} × 10^2)		Distribution coefficient (liters/kg)	
	I	II	I	II	I	II
1	0.08	0.08	1.26	1.34	0.82	0.71
2	0.07	0.09	0.74	0.62	0.53	0.56
3	0.12	0.14	0.76	0.83	0.74	0.65
5	0.10	0.17	0.90	0.86	0.96	0.87
6	0.17	0.10	1.03	1.08	0.60	0.71
7	0.14	0.10	0.92	0.81	0.61	0.51
8	0.08	0.09	0.96	0.88	0.64	0.70
9	0.12	0.14	0.99	0.90	0.88	0.91

lanine and tyrosine curves in the two investigations.

The urinary excretion of phenylalanine was negligible, less than 1% of the loading dose, in all experiments.

Discussion. The oral L-DOPA dose was given 45 min before the intravenous L-phenylalanine loading to obtain a high plasma DOPA concentration at the time of the phenylalanine injection (8). Under these conditions, L-DOPA had no effect on the distribution rate and metabolism of phenylalanine in parkinsonian patients treated with L-DOPA for 4–8 weeks. For the oral L-phenylalanine loading, the capsules of L-DOPA were given 30 min before the solution of L-phenylalanine, which gave a simultaneous absorption of the two amino acids. As judged from the plasma phenylalanine curve, L-DOPA strongly inhibited the absorption of L-phenylalanine and this effect was only seen when L-DOPA was given in close connection to the L-phenylalanine loading and was not found in patients who had not received L-DOPA for the last 12 hr. Whether the inhibitory effect of L-DOPA on the phenylalanine absorption gave not only a delayed but also an incomplete absorption can not settled from the present results.

The daily dietary intake of phenylalanine is about 2–5 g, *i.e.*, an amount similar to that of L-DOPA administered in treatment of parkinsonism. The present data show that 1 g of L-DOPA inhibited the intestinal absorption of 5–7 g of L-phenylalanine. As L-DOPA generally is taken with food this inhibition might be of clinical significance and especially in patients with a low protein intake. However, we have not observed any signs of amino acid deficiency in parkinsonian patients treated with L-DOPA for 1 to 2 years. This problem is at present being studied in our laboratory.

Summary. The effect of L-DOPA treatment on the absorption, distribution, and turnover rate of L-phenylalanine have been studied in 9 patients with parkinsonism. L-*DOPA*, when given with L-phenylalanine, reduced the absorption rate of this amino acid. This effect was only seen when L-DOPA and L-phenylalanine were given simultaneously. L-DOPA did not affect the plasma disappearance curve of intravenously injected L-phenylalanine. The theoretical distribution volume, the distribution rate, and turnover rate of L-phenylalanine were unaffected by the L-DOPA treatment.

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