Effect of Pyridoxine on Levodopa Metabolism in Normal and Parkinsonian Subjects (37370)

T. H. Hsu, J. R. Bianchine, T. J. Preziosi, and F. S. Messiha
(Introduced by F. J. Behal)

Johns Hopkins University School of Medicine, Baltimore, Maryland 21205 and Texas Tech University School of Medicine, Lubbock, Texas 79409

A high frequency of dose-dependent side effects often limits the therapeutic efficacy of Levodopa (L-DOPA) in the treatment of Parkinson's Disease (1). Inhibitors of peripheral aromatic L-amino acids decarboxylase have been utilized experimentally as adjunct therapy to L-DOPA in Parkinson's Disease (2–7). These inhibitors decrease the dose requirements of L-DOPA and certain side effects such as nausea and vomiting but do not alter the incidence of dyskinesias (2, 3, 5–7). Paradoxically, co-administration of pyridoxine with L-DOPA negates the therapeutic effect of L-DOPA (8, 9) but improves dopa-induced dyskinesia. Pyridoxine which is converted to pyridoxal 5-phosphate (vitamin B_6), a co-factor for enzymatic decarboxylation and transamination of aromatic L-amino acids, may accelerate metabolism of L-DOPA. To test this possibility, we studied the effect of pyridoxine administration on urinary excretion of DOPA and certain DOPA metabolites following administration of L-DOPA to normal and Parkinsonian subjects.

Material and Methods. (a) Clinical. Five consenting Parkinsonian patients, uncomplicated by cardiac, renal or hepatic disease, were admitted to the metabolic ward. These patients, ages 57–76, had been treated with L-DOPA, 3–6 g/day, during the previous two years. Their L-DOPA treatment was reduced to 2 g daily (0.5 g each 2 hr beginning at 8 AM) for seven days prior to pyridoxine administration. On Days 8 and 9, L-DOPA was continued at 2 g daily and pyridoxine was administered by mouth 50 mg each 4 hr beginning at 8 AM for a total daily dose of 150 mg. On Days 7 and 9, total urine output was collected serially, over acid, at 2, 4, 6, 8, and 24 hr.

Four healthy consenting volunteer men, ages 29–42, received progressively increased oral doses of L-DOPA from 0.5 to 2.0 g daily for seven consecutive days. On Days 8–15, oral L-DOPA was continued, 0.5 g at 2-hr intervals, beginning at 8 AM for a total daily dose of 2.0 g. On Days 14 and 15, pyridoxine was administered by mouth, 50 mg each 4 hr, for a total daily dose of 150 mg. On Days 13 and 15, urine was collected serially as described above. All urine specimens were collected in dark glass containers over 6 *N* hydrochloric acid.

(b) Chemical analyses. Urine samples were kept frozen at —20° until chemical analyses were made. The fractionation of urinary dopa and selected metabolites, *i.e.*, dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), were performed as previously described (10). The quantitative determination of DOPA, DA, DOPAC, and HVA utilized spectrofluorimetric methods (10–13). VMA was determined by the procedure of Pisano *et al.* (14). Data for DOPA and DA are given for hydrolyzed urine specimens and include both free and conjugates.

Results. The effects of pyridoxine administration on the urinary excretion of DOPA, DA, DOPAC, and HVA for the group of 5 Parkinsonian subjects are summarized in Table I. The data are expressed as Mean ± SD and are analyzed by *t* test for correlated means. Simultaneous administration of pyridoxine with L-DOPA decreased significantly the urinary excretion of DOPA from the base line which was obtained following administration of L-DOPA alone. This decrease in

TABLE I. Effect of Pyridoxine on the Cumulative Urinary Excretion of DOPA and Some Metabolites by Normal and Parkinsonian Subjects.

Subjects	Compound	Time interval (hr)	Cumulative urinary excretion (mg) mean ± SD: L-DOPA[a]	L-DOPA + pyridoxine[b]	p
Parkinsonian	DOPA	4	8.5 ± 2.2	3.8 ± 0.7	<0.01
		6	16.8 ± 4.0	9.8 ± 1.4	<0.02
		8	28.3 ± 4.9	18.1 ± 2.4	<0.01
		24	51.5 ± 4.3	35.5 ± 3.1	<0.02
	DA	4	18.4 ± 6.4	26.0 ± 9.6	<0.02
		6	37.6 ± 8.1	55.9 ± 18.0	<0.05
		8	68.6 ± 18.9	79.8 ± 3.4	<0.05
		24	150.3 ± 50.0	174.1 ± 51.8	<0.1 (n.s.)
	DOPAC	4	5.3 ± 2.3	14.2 ± 7.2	<0.05
		6	17.5 ± 8.6	34.5 ± 11.4	<0.02
		8	35.7 ± 15.0	62.0 ± 17.1	<0.01
		24	57.0 ± 26.0	95.3 ± 25.2	<0.02
	HVA	4	26.5 ± 12.4	33.2 ± 29.2	<0.05
		6	59.0 ± 27.3	112.5 ± 63.7	<0.1 (n.s.)
		8	104.8 ± 52.5	188.5 ± 113.3	<0.05
		24	211.0 ± 112.3	318.0 ± 172.5	<0.05
Normal	DOPA	4	8.8 ± 1.6	6.9 ± 2.1	n.s.
		6	13.3 ± 2.8	11.5 ± 2.1	n.s.
		8	18.8 ± 3.4	15.7 ± 1.5	n.s.
		24	35.4 ± 2.4	33.6 ± 1.6	n.s.
	DA	4	25.1 ± 5.1	22.3 ± 7.2	n.s.
		6	36.7 ± 8.1	36.0 ± 11.5	n.s.
		8	55.1 ± 9.6	46.2 ± 11.3	n.s.
		24	78.1 ± 8.7	65.5 ± 10.4	n.s.
	DOPAC	4	11.0 ± 4.0	11.2 ± 6.1	n.s.
		6	18.8 ± 9.4	18.9 ± 8.1	n.s.
		8	25.6 ± 12.7	26.4 ± 1.1	n.s.
		24	27.9 ± 12.3	27.0 ± 1.1	n.s.
	HVA	4	80.5 ± 36.3	118.9 ± 52.9	n.s.
		6	158.9 ± 17.1	187.0 ± 62.2	n.s.
		8	194.0 ± 110.8	252.3 ± 63.3	n.s.
		24	321.2 ± 32.5	322.5 ± 73.3	n.s.

[a] L-DOPA administered 0.5 g by mouth each 2 hr beginning at 8 AM (time zero) for a total daily dose of 2.0 g.

[b] Pyridoxine—50 mg by mouth each 4 hr for a daily dose of 150 mg was co-administered with L-DOPA as described above on selected days.

DOPA excretion was approximately 40% at the initial 4-hr period and remained significantly decreased throughout the entire 24 hr studied.

Further, co-administration of pyridoxine with L-DOPA exerted a marked increase in DA excretion from treatment period with L-DOPA alone. This DA increase from a base line of 18.4 ± 6.4 μg to 26.0 ± 9.6 μg at the initial 4-hr period was significant ($p < 0.02$). However, the cumulative DA excreted at the 6 and 8-hr intervals indicate

only a marginal significance ($p < 0.05$). Overall, pyridoxine treatment did not increase significantly the total 24-hr output of DA. Co-administration of pyridoxine with L-DOPA increased significantly DOPAC excretion by 2.7-fold and 1.7-fold at the 4 and 24-hr periods, respectively. HVA excreted in urine was increased by approximately twofold during pyridoxine treatment at the 4-hr period. Total mean urinary HVA excreted during the 24 hr increased from 211.0 ± 112.3 mg prior to pyridoxine treatment to 318.0 ± 172.5 mg/24 hr post pyridoxine treatment ($p < 0.05$).

The effects of pyridoxine on the metabolism of L-DOPA in four normal adult males indicate no significant alteration in urinary excretion of DOPA, DA, DOPAC, and HVA during periods studied. VMA remained unchanged during pyridoxine treatment from baseline values for both normal and Parkinsonian subjects studied.

In this study, simultaneous administration of pyridoxine with L-DOPA, to the Parkinsonian patients, resulted in deterioration of the Parkinson's symptoms in two of the five patients. These two patients manifested increased tremor which persisted for 24 hr after discontinuation of pyridoxine. The normal subjects did not demonstrate any neurological side effects during the entire metabolic study.

Discussion. Simultaneous administration of pyridoxine with L-DOPA to our Parkinsonian patients significantly decreased the amount of DOPA excreted in urine and concomitantly increased urinary DA excretion. Previous reports indicate that co-administration of pyridoxine with L-DOPA to Parkinsonian patients markedly decreased peak plasma DOPA concentrations (15–17). However, administration of pyridoxine with levodopa to Parkinsonian patients decreased the amounts of DOPA and DA excreted in urine from treatment period with levodopa at 8 hr with little changes in DOPAC and HVA excretion (15). These results derived at 8 hr of drug treatment may not detect earlier metabolic changes. Further, levodopa dose administered varied from 1.0 to 5 g/day for the four patients studied while pyridoxine administration was maintained at a lower fixed dosage of 50 mg resulting in an unequal dose ratio between levodopa and pyridoxine (15). On the other hand, it has been shown (17) that administration of pyridoxine concomitant with levodopa to Parkinsonian patients produced a 3.5-fold increase in plasma concentration of DOPA relative to DA which suggested an enhanced extracerebral decarboxylation of levodopa by pyridoxine (17). Moreover, we have found that administration of pyridoxine during treatment with levodopa and carbidopa (MK-486) to two Parkinsonian patients, initially decreased the excretion of levodopa major metabolites and thus failed to increase the same as without carbidopa (18). The latter exert an inhibitory effect on extracerebral decarboxylation of levodopa (19, 20). All these findings are compatible with the postulate that pyridoxine enhances or accelerates the decarboxylation of DOPA to DA and may explain the mechanism by which pyridoxine negates the therapeutic efficacy of levodopa.

Since pyridoxal-5-phosphate, the biological active form of pyridoxine, is a cofactor for DOPA decarboxylase, pyridoxine may augment the conversion of DOPA to DA and, therefore, decrease availability of L-DOPA to the central nervous system. In a recent study of a single Parkinsonian patient (21), a decreased HVA concentration in cerebrospinal fluid associated with worsening of Parkinsonian symptoms followed co-administration of pyridoxine and L-DOPA. Interestingly, administration of pyridoxine to Parkinsonian patients treated with L-DOPA and an inhibitor of dopa decarboxylase did not reverse the therapeutic effects of L-DOPA (21).

Simultaneous administration of pyridoxine with L-DOPA to our normal subjects did not alter the amounts of dopa and metabolites determined in urine. This contrasts with the findings in Parkinsonians noted above. Important differences between these two groups include the advanced age and chronic administration of Levodopa to the Parkinsonian patients studied. Accordingly, chronic ingestion of Levodopa might decrease pyridoxine content in the extracerebral tissue, saturate the peripheral pool of aromatic L-amino acids decarboxylase, and decrease activity of cer-

tain catecholamine metabolizing enzymes such as catechol-O-methyl transferase (22). It seems, therefore, that the mechanism by which pyridoxine antagonizes L-DOPA therapy, in chronically treated patients, is associated with enhancement in the peripheral metabolism of L-DOPA. However, the formation of Schiff-base and/or condensation product of dopa and pyridoxine may possibly inhibit other enzymes involved in metabolism of L-DOPA.

Summary. The effect of pyridoxine on the metabolism of Levodopa was studied in four normal volunteer subjects and five Parkinsonian patients. Each subject served as his own control. Co-administration of Levodopa and pyridoxine in Parkinsonian patients, but not in healthy subjects, significantly decreased DOPA excreted in urine and concomitantly increased urinary DA and DOPAC. Clinically worsened symptoms followed co-administration of pyridoxine and Levodopa in two of five Parkinsonians studied. These data suggest that pyridoxine enhances extracerebral metabolism of Levodopa in chronically treated Parkinsonian patients.

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