

Failure of vitamin B₆ to reverse the L-dopa effect in patients on a dopa decarboxylase inhibitor

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SUMMARY Seven patients with Parkinsonism previously on L-dopa were placed on a regimen of L-dopa and alpha methyl dopa hydrazine (a dopa decarboxylase inhibitor). Two of these patients had previously shown marked clinical deterioration of the L-dopa improvement when given pyridoxine. None of the seven patients receiving alpha methyl dopa hydrazine demonstrated any change in their condition when given pyridoxine. The failure of vitamin B₆ to reverse the clinical effect of L-dopa in patients receiving both L-dopa and a peripheral dopa decarboxylase inhibitor suggests that reversal of the L-dopa effect induced by vitamin B₆ is due to increasing the activity of the enzyme dopa decarboxylase outside the central nervous system.

In patients with Parkinsonism receiving L-dopa (L-3, 4-dihydroxyphenylalanine), vitamin B₆ has recently been shown to cause a loss or reversal of the L-dopa effect (Duvoisin, Yahr, and Coté, 1969; Yahr, Duvoisin, Schear, Barrett, and Hoehn, 1970). This was discovered when Duvoisin *et al.* (1969) gave vitamin B₆ to patients receiving L-dopa in an attempt to increase formation of dopamine from L-dopa within the central nervous system (CNS) and thereby increase the efficacy of L-dopa. Decarboxylation of L-dopa to dopamine is carried out by a single enzyme, dopa decarboxylase (L-aromatic amino acid decarboxylase). This enzyme is dependent upon the presence of vitamin B₆ to carry out its function (Lovenberg, Weissbach, and Udenfriend, 1962; Sourkes, 1966). There is at the present time no explanation as to why a cofactor (B₆), which is necessary for conversion of dopa to dopamine, when given in excessive amounts actually inhibits the clinical effects of L-dopa. At least two different possible mechanisms could explain this. Pyridoxine in excessive amounts could increase the activity of dopa decarboxylase in the periphery. This would increase the metabolism of L-dopa, lower L-dopa blood levels, and decrease the penetration and metabolism of L-dopa within the central nervous system. It is also possible that pyridoxine could act through a mechanism not involving dopa decarboxylase.

We have evaluated the effects of pyridoxine on patients receiving both L-dopa and a dopa decarboxylase inhibitor, MK-486 (alpha methyl dopa

hydrazine). These observations help to explain the paradoxical effects of large amounts of pyridoxine in patients receiving L-dopa.

METHODS AND RESULTS

Seven patients with Parkinsonism who had been on L-dopa for at least one year were included in this study. These patients ranged in age from 43 to 67 with an average age of 57 years. The patients had had Parkinsonism for an average of seven years with a range of from four to 11 years. The patients had been evaluated according to the criteria of Hoehn and Yahr (1967). Before the initiation of L-dopa, one patient was felt to be in stage II (bilateral involvement, minimal functional impairment) five stage III (impaired righting reflexes), and one in stage IV (severe involvement but able to walk and stand unassisted).

The disability of each patient was estimated according to the Northwestern Disability Scale (Canter, de la Torre, and Mier, 1961). This is a scale which grades the patient's disability in six separate categories. Each category (walking, dressing, eating, feeding, hygiene, and speech) is graded numerically and the sum of the six is taken as the total disability. In our study the patient's disability ranged from 6 to 24 with an average of 19 (Table 1).

The patients were on L-dopa for an average of 22 months. The dose ranged from 3.5 to 9 g/day with an average of 6.4 g/day. The improvement in each individual was calculated by subtracting level of

TABLE 1
DISABILITY OF PATIENTS

Subject	Age (yr.)	Sex	Duration of disease (yr.)	Stage	Disability	Duration on L-dopa (yr.)	Disability* on L-dopa and dose (g)	Pyridoxine: amount (mg/day)	Change in disability	Duration of disability (wk.)
FB	55	M	11	III	20	2	6 (8)	5 (7)	6-14	3
FW	62	F	9	IV	24	2	12 (4-5)	10 (4)	12-21	3
EK	43	F	4	II	6	1	3 (3-5)			
DS	46	M	8	III	21	2	7 (8)			
DC	67	M	6	III	20	2	8 (5)			
HP	63	M	6	III	24	2	10 (7)			
JS	65	M	5	III	18	2	6 (9)			

*Northwestern Disability Scale.

disability while on L-dopa from the pretreatment level. This number divided by the initial level of disability was taken as the degree of improvement.

Percent improvement =

$$\frac{\text{Initial disability} - \text{disability on L-dopa}}{\text{Initial disability}} \times 100$$

In this study the disability after L-dopa averaged 7.4 with a range of 3 to 12. This represents an average of 61% improvement after L-dopa. Two patients had taken vitamin B₆ while on L-dopa. The first received 5 mg/day for one week. The patient's disability increased from 6 to 14. The degree of improvement of pre-L-dopa disability decreased from 70% to 30%. The patient noted increased hesitation in initiating walking and marked propulsion and retro-pulsion of gait. He found it more difficult getting in and out of a chair and his voice became slower and more monotonous. After the vitamin B₆ was discontinued, he slowly improved over two to three weeks to his previous level of disability.

The second patient inadvertently took 10 mg/day of vitamin B₆ for four days while on L-dopa. Before any therapy had been given the patient had been unable to get out of a chair or turn over by herself. Her speech was severely affected. While on L-dopa her disability improved by 50% (from 24 to 12). After receiving vitamin B₆ the patient had a return of all previous symptoms with an increase in disability to 21, or only 12.5% improvement from her condition before L-dopa. The patient recovered slowly but completely to 50% improvement level three weeks after discontinuing the vitamin B₆.

There was no justification for giving the remaining five patients vitamin B₆ while on L-dopa alone because of the three week loss of benefit produced in the above two patients and because pyridoxine has been shown to produce similar deleterious effects in almost all patients with Parkinsonism on L-dopa (Duvoisin *et al.*, 1969).

All patients were started on 200 mg/day of MK-486 (alpha methyl dopa hydrazine) a peripheral dopa decarboxylase inhibitor (Cotzias, Papavasiliou, and Gellene, 1969). This was given to decrease peripheral side-effects of L-dopa that had limited the efficacy of treatment in these patients. These side effects included anorexia, nausea, vomiting, palpitations, and uneven effect of medication during the day (Table 2). The average dose of L-dopa required fell from 6.4 g to 1.7 g/day. Disability decreased from 7.4 when on L-dopa alone to 5.6 after MK-486 was added. This represented a further increase in per cent improvement from 61% to 71%. The efficacy of L-dopa was either maintained or improved, while the dose of L-dopa was markedly decreased. This suggests that the MK-486 did in fact decrease the peripheral destruction of L-dopa in these patients and allow the same central effect of the L-dopa with lower doses. This suggests that the agent did block peripheral dopa decarboxylase in the doses given to these patients.

All patients were given 100 mg vitamin B₆ for one or two days after having been on MK-486. None of these patients showed any change in disability (Table 2) or physical status after receiving the pyridoxine.

DISCUSSION

L-Dopa, a naturally occurring amino acid, is the normal precursor of dopamine and the other important physiological catecholamines, noradrenaline and adrenaline. It is decarboxylated to dopamine by the enzyme dopa decarboxylase, an enzyme dependent on pyridoxine for its function (Lovenberg *et al.*, 1962; Sourkes, 1966). The enzyme decarboxylates a variety of other substrates, including L-tryptophan to serotonin (5-HT) and is frequently referred to as L-aromatic amino acid decarboxylase. Loss of dopamine within the striatum is considered

TABLE 2
EFFECTS OF MK 486

Subject	Duration on L-dopa (yr.)	Dose of L-dopa (g)	Reason for adding MK 486	Disability* on:		Dose of		Effect of 100 mg/day vit B ₆	Side-effects on MK 468 and L-dopa
				L-dopa	MK 486	L-dopa (g)	MK 486 (mg)		
FB	2	8	a, d, c	6	4	105	200	No change	a, d, improved; c, worse
FW	2	4.5	a, b, d	12	12	1.2	200	No change	a, b, improved; d, unchanged
EK	1	3.5	a, b, d	3	2	75	200	No change	a, b, improved; d, unchanged
DS	2	8	d	7	3	2.0	200	No change	d, improved;
DC	2	5	a, b, d	8	6	1.7	200	No change	a, b, improved; d, unchanged
HP	2	7	a, d	10	8	2.5	200	No change	a, improved; d, unchanged
JS	2	9	a, b, c	6	4	2.0	200	No change	d, unchanged a, b, c, improved

a: anorexia, nausea, vomiting;
b: weight loss;
c: palpitations;
d: uneven effect;
e: dyskinesias.

*Northwestern Disability Scale.

to be related to the development of the signs and symptoms of Parkinsonism (Hornykiewicz, 1966). Dopamine is unable to cross the blood-brain barrier so that the dopamine loss of Parkinsonism cannot be corrected by giving the patient dopamine. L-Dopa, if given in sufficient amounts, can cross the blood-brain barrier and be converted to dopamine at the blood-brain barrier and within the brain (Bertler, Falck, Owman, and Rosengrenn, 1966). It is generally accepted that the therapeutic efficacy of L-dopa is due to the increased amounts of dopamine formed within the blood-brain barrier (Hornykiewicz, 1966; Klawans, 1968).

L-Dopa therapy increases the cerebrospinal fluid (CSF) homovanillic acid (HVA) levels. HVA is the major catabolic product of dopamine. The concentration of HVA in the CSF reflects dopamine metabolism within the CNS. In Parkinsonism, the HVA is generally decreased. After oral L-dopa therapy, there is marked increase in the CSF HVA level (Weiner, Harrison, and Klawans, 1969). This is more direct evidence of increased dopamine metabolism in the CNS of patients with Parkinsonism receiving L-dopa.

Because the conversion of L-dopa to dopamine is mediated by a pyridoxine dependent enzyme, Duvoisin *et al.* (1969) administered large doses of pyridoxine to Parkinsonism patients receiving L-dopa in hope of enhancing the efficacy of L-dopa. Instead, they noted a rapid reversal of the beneficial effects of L-dopa. As little as 10 mg pyridoxine was noted to decrease the efficacy of L-dopa. When the pyridoxine was withdrawn, the patients slowly improved.

Degkwitz, Frowein, Kulenkampff, and Mohs (1960) found that pyridoxal phosphate potentiated the vasopressor effect of L-dopa in man. As this effect is produced by catecholamines formed from L-dopa and not by L-dopa itself, they suggested that pyridoxal phosphate stimulated an increase in peripheral dopa decarboxylase activity resulting in an increased rate of formation of peripheral dopamine and other catecholamines.

Klawans, Ilahi, and Shenker (1970) suggest that in Parkinsonism, pyridoxine produces its adverse effect by increasing the peripheral metabolism of dopa to dopamine and thereby decreasing the amount of dopa available to cross the blood-brain barrier to produce its central effect. This concept is supported by a patient described by Klawans (1971). The patient, while on 3 g L-dopa daily, was placed on 10 mg/day vitamin B₆. Her clinical condition, which had begun to improve while on L-dopa, deteriorated to pre-L-dopa state after the vitamin B₆ was given. Her CSF HVA after three days on B₆ was 17 ng/ml. compared with 24 ng/ml. before institution of therapy with L-dopa. This was the only case of a sample of 53 patients with Parkinsonism where CSF HVA fell while receiving L-dopa. It suggests that the simultaneous administration of vitamin B₆ and L-dopa interferes with the effect of L-dopa on cerebral dopamine metabolism as estimated by CSF HVA levels.

If the effect of pyridoxine is secondary to increased peripheral decarboxylase activity, then the administration of a peripheral dopa decarboxylase inhibitor should prevent pyridoxine reversal of the beneficial

effects of L-dopa. Bartholini, Burkaard, Pletscher, and Bates (1967) showed that RO 4-4602 a strong inhibitor of aromatic amino acid decarboxylase, would in low doses inhibit only peripheral decarboxylase. This has been used clinically with lower doses of L-dopa and has been shown to reduce markedly the number and severity of peripheral side-effects, such as nausea, vomiting, postural hypotension, and cardiac arrhythmias (Barbeau and Gillo-Joffroy, 1969; Tissot, Gaillard, Guggisberg, Gauthier, and Ajuriaguerra, 1969). Cotzias *et al.* (1969) reported similar results with another peripheral dopa decarboxylase inhibitor, alpha methyl dopa hydrazine. In the present study seven patients on a regime of L-dopa and alpha-methyl dopa hydrazine were placed on large doses (100 mg/day) of pyridoxine. All seven patients failed to show any deterioration in their clinical condition when these large doses of vitamin B₆ were given. Two of these patients had been placed on vitamin B₆ in smaller doses when only on L-dopa and the B₆ produced a marked reversal of the L-dopa effect. This suggests that the adverse effect of pyridoxine was blocked by peripheral dopa decarboxylase inhibition.

Further evidence supporting the peripheral mechanism of pyridoxine is seen in tardive dyskinesia, a hyperkinetic movement disorder which usually occurs in elderly people who are on large doses of neuroleptic agents, especially phenothiazines, and which persists after the discontinuation of the drug. It is suggested that phenothiazines, by blocking dopamine receptors and producing a prolonged chemical denervation, result in receptor site hypersensitivity to dopamine with the production of abnormal movements when dopamine is able to reach these receptors (Klawans, 1970). L-Dopa has been shown to make these movements worse, while dopaminergic blocking agents improve them (Klawans and McKendall, 1971). Since agents which alter dopamine activity at dopamine receptor sites alter tardive dyskinesia, it is reasonable to view tardive dyskinesia as a sensitive index for either increased or decreased central dopamine effect. Recently Crane, Turek, and Kurland (1970) demonstrated the failure of pyridoxine to reduce dyskinesic movements in nine patients with tardive dyskinesias. The failure of these movements to improve or worsen with pyridoxine suggests that pyridoxine does not affect dopaminergic activity in these patients. This implies that vitamin B₆ does not decrease the amount of dopamine acting at dopamine receptors in patients who have normal dopamine turnover and are not receiving L-dopa. This is not surprising, since the natural amino acid source for brain dopamine is tyrosine and not L-dopa.

Since L-aromatic amino acid decarboxylase also

decarboxylates L-tryptophan to form serotonin, vitamin B₆ would similarly be expected to diminish the effect of central serotonin. Bowers (1970) administered L-tryptophan and vitamin B₆ to 15 psychiatric patients and observed mental status and CSF 5 hydroxy indole acetic acid (5-HIAA) levels as a measure of brain serotonin synthesis. The behavioural changes were very mild and not clinically significant. The changes in CSF 5-HIAA were also small, in five cases actually decreasing after receiving L-tryptophan. This decrease is analogous to the decrease in HVA found in the Parkinsonism patient placed on vitamin B₆ (Klawans, 1971) and suggests that pyridoxine may have decreased central serotonin by increasing peripheral metabolism of 5-HTP to serotonin.

The precise mechanism by which vitamin B₆ increases dopa decarboxylase activity is unknown. A similar activation of enzyme systems by vitamin B₆ has been described in cystathioninuria (Frimpter, 1966). Large doses of vitamin B₆ largely correct the inability of the apoenzyme cystathioninase to cleave the amino acid cystathionine. Vitamin B₆ apparently acts as a coenzyme to activate the apoenzyme cystathioninase. It is hypothesized that a defect in the apoenzyme molecule is partially compensated for by large doses of vitamin B₆. Similarly, in primary hyperoxaluria, Gibbs and Watts (1969) noted that large doses of pyridoxine hydrochloride reduced the urinary oxalate excretion and suggested that vitamin B₆ may be acting by inducing apoenzyme synthesis.

While the action of vitamin B₆ on dopa decarboxylase may be as a coenzyme, alternative hypotheses have been proposed. Dopa decarboxylase may be an allosteric enzyme (Monod, Changeux, and Jacob, 1963) with which vitamin B₆ functions as an activating effector on the allosteric site of the molecule. Dopa decarboxylase could also be an inducible enzyme (Jacob and Monod, 1961) in which case vitamin B₆ could increase the synthesis of dopa decarboxylase by inducing the genetic mechanism responsible for its formation. Vitamin B₆ presumably would combine allosterically with normal repressor protein and prevent it from inhibiting the genetic mechanism responsible for dopa decarboxylase synthesis. Phenobarbitone is known to induce enzymes in this manner, and in some patients phenobarbitone has reversed the therapeutic effect of L-dopa. (Klawans *et al.*, 1970, Mandell, personal communication). This suggests that the adverse effects of both phenobarbitone and vitamin B₆ upon L-dopa therapy may be mediated through an increase in dopa decarboxylase function due to enzyme induction. In a case of infantile subacute necrotizing encephalopathy, Ebadi, Bostad, and Pellegrino (1969) found that in spite of an increase in the 24

hour urinary excretion of dopamine, the dopamine concentration of the striatum was markedly decreased. This was explained by a selective inhibition of dopa decarboxylase in the brain. Since the infant received large doses of pyridoxine, it is more likely that the pyridoxine induced apoenzyme synthesis and conversion of dopa to dopamine peripherally. The well-described substantia nigral lesions (Greenhouse and Schneck, 1968) seen in this condition account for the decreased central dopamine and are probably unrelated to any peripheral mechanism.

Other possible mechanisms suggested by Duvoisin *et al.* (1969) by which pyridoxine may alter dopa metabolism include Schiff base formation, increased transamination of dopa, and possible acceleration of nonenzymatic conversion of dopa to dopamine in the periphery. All of these would still be operative in patients on L-dopa and alpha methyl dopa hydrazine. The fact that alpha methyl dopa hydrazine prevents the reversal of L-dopa effect by vitamin B₆ suggests that B₆ reversal must work through peripheral dopa decarboxylase and not by combination of vitamin B₆ with L-dopa (Schiff base formation) other enzymatic mechanisms (transamination) or nonenzymatic dopa catabolism.

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