Norepinephrine Precursor Therapy in Neurogenic Orthostatic Hypotension

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Background—In patients with neurogenic orthostatic hypotension (NOH), the availability of the sympathetic neurotransmitter norepinephrine (NE) in the synaptic cleft is insufficient to maintain blood pressure while in the standing posture.

Methods and Results—We determined the effect of oral administration of the synthetic amino acid L-threo-3,4-dihydroxyphenylserine (L-DOPS), which is decarboxylated to NE by the enzyme L–aromatic amino acid decarboxylase (L-AADC) in neural and nonneural tissue, on blood pressure and orthostatic tolerance in 19 patients with severe NOH (8 with pure autonomic failure and 11 with multiple-system atrophy). A single-blind dose-titration study determined the most appropriate dose for each patient. Patients were then enrolled in a double-blind, placebo-controlled, crossover trial. L-DOPS significantly raised mean blood pressure both supine (from 101±4 to 141±5 mm Hg) and standing (from 60±4 to 100±6 mm Hg) for several hours and improved orthostatic tolerance in all patients. After L-DOPS, blood pressure increases were closely associated with increases in plasma NE levels. Oral administration of carbidopa, which inhibits L-AADC outside the blood-brain barrier, blunted both the increase in plasma NE and the pressor response to L-DOPS in all patients

Conclusions—Acute administration of L-DOPS increases blood pressure and improves orthostatic tolerance in patients with NOH. The pressor effect results from conversion of L-DOPS to NE outside the central nervous system. (Circulation. 2003;108:724-728.)

Key Words: nervous system, autonomic ■ blood pressure ■ vasoconstriction ■ norepinephrine ■ receptors, adrenergic, alpha

Neurogenic orthostatic hypotension (NOH) results from decreased delivery of the sympathetic neurotransmitter norepinephrine (NE) to vascular adrenergic receptors, either because of blunted central nervous system drive or impaired function of postganglionic sympathetic neurons. The effectiveness of the dopamine precursor dihydroxyphenylalanine (DOPA) to treat Parkinson disease1 suggested that a precursor of NE might successfully treat NOH.2 A synthetic precursor of NE, dihydroxyphenylserine (DOPS) (Figure 1), reverses NOH in the rare syndrome of dopamine β hydroxylase (DBH) deficiency.3,4 However, initial small or uncontrolled trials in patients with NOH attributable to degenerative disorders showed a significant pressor response in some but not all studies.5-11

We hypothesized that several factors might explain these conflicting results. First, many patients with NOH have parkinsonism and were treated with a combination of L-dihydroxyphenylalanine (L-DOPA) and carbidopa; carbidopa is a peripheral L–aromatic amino acid decarboxylase (L-AADC) inhibitor that could prevent NE formation from DOPS outside the brain, potentially blunting its pressor effect. Second, most studies used a racemic mixture that contains both the D and L isoforms of DOPS, but only the L isoform is decarboxylated to biologically active L-NE. Furthermore, the D-stereoisomer of DOPS might inhibit the decarboxylation of the L stereoisomer to L-NE, thereby attenuating the pressor effect.12

We conducted a study to determine whether the pure L stereoisomer of DOPS (L-DOPS) could be converted to NE, raise blood pressure, and improve orthostatic tolerance in patients with NOH attributable to degenerative disorders. To minimize intersubject differences attributable to varying degrees of adrenergic receptor supersensitivity, each patient’s dose of L-DOPS was first individualized in a dose-ranging trial. We then performed a double-blind, crossover, placebo-controlled trial. In a separate trial, we examined the effect of carbidopa administered together with L-DOPS on blood pressure and NE generation. Finally, we investigated the pharmacokinetics of L-DOPS and the generated NE and

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L-DOPS

DOPAMINE

NOREPINEPHRINE

Figure 1. Pathway for the physiological synthesis of norepinephrine from L-DOPA and nonphysiological synthesis of nor-epinephrine from L-DOPS.

determined the relationship between the pressor response and venous plasma NE levels.

Methods

Study Population
We studied 19 subjects (age 64 ± 2 years, mean ± SE; 4 women and 15 men) with severe symptomatic orthostatic hypotension, defined as a consistent decrease in systolic/diastolic blood pressure of more than 20/10 mm Hg on standing and daily episodes of presyncope or syncope. Eleven had multiple system atrophy (MSA), a disorder characterized by a combination of parkinsonism and cerebellar and autonomic deficits, and 2 had predominantly cerebellar dysfunction (formerly known as olivopontocerebellar atrophy type). MSA and PAF patients were of similar age (61 ± 10 versus 67 ± 8 years, mean ± SE; P = 0.17) and gender (MSA, 10 men and 1 woman; PAF, 5 men and 3 women; P = 0.13). Patients with sustained, severe hypertension (180/110 mm Hg in the sitting position), clinically significant coronary artery, cerebrovascular, and peripheral vascular disease, or cardiac arrhythmias were excluded from the study. The institutional review boards of Mount Sinai School of Medicine and Beth Israel Deaconess Medical Center approved the project, and all patients signed an informed consent.

Study Preparation
Patients were admitted to the Clinical Research Center of the Mount Sinai Medical Center (New York, NY) or Beth Israel Deaconess Medical Center (Boston, Mass). In the week preceding admission and throughout the study, subjects consumed a diet containing at least 100 mEq sodium, 75 mEq potassium, and 1.5 L of fluid intake per day. Daily caloric intake was 2200 to 2500 calories for male and 1800 to 2300 calories for female patients. The diet was free of catecholamine and methylxanthine derivatives. Patients were taking 9-α-fludrocortisone before the study and continued taking it throughout the study at the prestudy dosages (0.1 to 0.2 mg/d). Other medications affecting the autonomic nervous system, including L-DOPA/carbidopa, which was taken by 4 patients, were discontinued at least 5 half-lives before the studies. Sumitomo Pharmaceuticals (Japan) supplied L-DOPS but did not provide financial support, design the study, collect or analyze the data, or write any part of this report.

Dose-Ranging Study
The optimal dose of L-DOPS for each patient was determined in a single-blind, dose-ranging study. Patients received 200 mg of L-DOPS at 7 AM on day 1, followed by 400, 1000, 1600, and 2000 mg of L-DOPS at the same time on subsequent days. Blood pressure (BP) and heart rate (HR) were measured using an automatic arm cuff (Critikon Dinamap 1846SX/P) in the supine position, and 1 and 3 minutes after sitting and standing. BP and HR measurements were made 30 minutes before L-DOPS administration. Subsequent measurements were made at 30-minute intervals for 6 hours and then every hour for 6 hours. Patients were supine for 10 minutes before each set of BP measurements. A standard breakfast was served 1 hour before medication ingestion, and a standard lunch was served at 1 PM. The dose-ranging study was terminated if (1) the orthostatic fall in systolic BP after 3 minutes of standing was consistently <20 mm Hg, (2) a systolic BP of 180 mm Hg or diastolic BP of 110 mm Hg for 3 minutes of standing was present consistently, (3) sustained supine systolic BP of >200 mm Hg or sustained supine diastolic BP of >110 mm Hg was observed, or (4) when a maximum dose of 2000 mg of L-DOPS was reached.

Double-Blind, Placebo-Controlled, Crossover Study
In this 3-day study, each patient received the dose of L-DOPS determined in the dose-ranging study (doses ranged from 200 to 2000 mg; mean dose ± SE was 1137 ± 131 mg). On days 1 and 3, either L-DOPS or placebo was given at 7:00 AM. Day 2 was a washout day. BP and HR were monitored as described above (see dose-ranging study). The sequence of drug administration was randomized by the pharmacists at each institution. Identically colored capsules were dispensed on each day to maintain the double-blind nature of the study.

Carbidopa Study
To determine the effect of the peripheral l-aromatic amino acid decarboxylase inhibitor, carbidopa, on the pressor and NE responses to L-DOPS, a separate 3-day trial was conducted after the double-blind trial (n = 6; 3 men and 3 women; 2 MSA, 4 PAF; age 63 ± 4 years, mean ± SE). Subjects received L-DOPS alone on day 1, followed by 200 mg of carbidopa alone on day 2 and 200 mg of carbidopa combined with L-DOPS on day 3. Patients received the same dose of L-DOPS as in the double-blind trial. Medications were given at 7:00 AM. To ensure decarboxylase inhibition, on day 3 carbidopa was administered at 5:15 AM followed by L-DOPS at 7:00 AM. A standard breakfast was given at 6:00 AM. BP and HR were monitored as described above (see dose-ranging study). NE levels were determined from arm venous plasma samples drawn in the supine position through an indwelling catheter. Blood samples were collected 7 times (at 5:00 AM, 6:45 AM, 7:30 AM, 8:00 AM, 9:00 AM, 10:00 AM, and 1:00 PM) on days 1 and 3.

Pharmacokinetic Study
To determine the pharmacokinetics of L-DOPS and its effects on plasma NE levels, blood was drawn at 6:45 AM, 15 minutes before receiving a single dose of 400 mg of L-DOPS. Blood was drawn again after 0.5, 1, 2, 3, 6, 12, 24, and 48 hours. All blood samples were taken after 10 minutes in the supine position through a 21-gauge catheter with a heparin lock in an antecubital vein. BP and HR were measured as described above (see dose-ranging study). Plasma levels of L-DOPS and NE were assayed by alumina extraction followed by liquid chromatography with electrochemical detection in the same laboratory for all patients.

Statistical Analysis
All patients enrolled in the double-blind crossover trial completed the study. The primary analysis of the data was an intention-to-treat analysis comparing the effect of L-DOPS or placebo on BP supine and standing. The primary variables were BP and HR (supine and after standing for 1 and 3 minutes) and ability to remain standing for 3 minutes (ie, orthostatic tolerance). The results were analyzed using 2-factor ANOVA with repeated measures. Separate ANOVA models were used to assess differences between treatments and between diagnostic groups, time being a factor in all analyses. Venous plasma levels of L-DOPS and NE were analyzed using a one-way ANOVA with repeated measures. Post hoc testing using Bonferroni correction was performed whenever results of the ANOVA were significant.
binary data were evaluated by a χ² test. Results with P<0.05 were considered statistically significant.

Results

Hemodynamic Response to L-DOPS

Administration of L-DOPS increased BP in all patients both while supine and after standing for 1 and 3 minutes (P<0.001 versus placebo) (Figure 2). The pressor effect began 1 hour after L-DOPS administration and lasted 6 hours while standing and 8 hours while supine. The peak standing BP occurred 3.5 hours after L-DOPS administration (P<0.0001 versus placebo).

HR remained unchanged after L-DOPS or placebo administration while supine (71±3 to 78±3 versus 72±3 to 74±2 bpm), after standing for 1 minute (79±3 to 83±3 versus 81±3 to 81±3 bpm), and after standing for 3 minutes (83±3 to 85±3 versus 80±3 to 82±3 bpm), L-DOPS versus placebo, mean±SE, P=NS.

Patients could stand for the 1-minute BP determination 96% of the time after receiving either L-DOPS or placebo (P=NS). For the 3-minute BP measurement, patients were able to stand 94% of the time after receiving L-DOPS but only 84% of the time after receiving placebo (P<0.001).

Hemodynamic Effect of L-Aromatic Amino Acid Decarboxylase Inhibition

To determine whether the increase in BP elicited by L-DOPS was attributable to its metabolism to NE inside or outside the central nervous system, we used carbidopa, an inhibitor of L-AADC that does not cross the blood-brain barrier. As shown in Figure 3, ingestion of carbidopa abolished the pressor responses to L-DOPS. BP and HR were similar when patients were treated with placebo, carbidopa alone, and carbidopa with L-DOPS.

Responses in MSA and PAF

Before L-DOPS ingestion, MSA and PAF patients had similar BPs and HRs while supine and standing. The mean dose of L-DOPS in the MSA group was 1327±133 mg (mean±SE), and in the PAF group 875±230 mg (P=NS). The mean weight of the MSA and PAF patients was similar (78±4 versus 77±7 kg, mean±SE). When compared with placebo, after L-DOPS administration, systolic BP in the supine position increased more in patients with PAF than in patients with MSA (59±10 mm Hg in PAF versus 40±7 mm Hg in MSA, mean±SE, P<0.05). There was a trend toward higher systolic BP in patients with PAF after 1 minute in the standing position, but this did not reach statistical significance.
L-DOPS and Norepinephrine Plasma Levels

The peak L-DOPS level, 1942±224 ng/mL (mean±SE), was attained 3 hours after dosage (P<0.001). L-DOPS remained detectable for at least 22 hours. Plasma NE increased from the baseline level of 294±80 to 806±235 pg/mL (P<0.05) 2 hours after L-DOPS administration. NE peaked at 1250±208 pg/mL 6 hours after L-DOPS ingestion (P<0.005) (Figure 4). Plasma levels of NE remained significantly elevated for at least 46 hours. As shown in Figure 5, the threshold NE venous plasma level required to exert a pressor effect in patients with NOH was 700 pg/mL.

After concomitant administration of L-DOPS with carbidopa, plasma levels of L-DOPS were higher than when L-DOPS was administered without carbidopa (4556±1011 versus 1942±224 ng/mL, P<0.01). In addition, carbidopa markedly attenuated the increase in plasma NE levels. Six hours after concomitant L-DOPS and carbidopa administration, the venous plasma NE level had only increased from 216±125 to 407±271 pg/mL, compared with the increase from 294±80 to 806±235 pg/mL after L-DOPS alone (P<0.05).

Adverse Events

L-DOPS was well tolerated by all patients, and there were no permanent side effects. The frequency of supine hypertension (systolic BP >180, diastolic BP >110 mm Hg, or both) was higher after L-DOPS than after placebo (45% versus 23% of BP measurements, P<0.00001). After receiving L-DOPS, the frequency of supine systolic and diastolic hypertension was similar in MSA and PAF patients. However, on placebo, diastolic, but not systolic, supine hypertension was more common in MSA patients than in PAF patients (25% versus 3%, P<0.05). One patient had hyponatremia, which reversed after saline infusion. Another patient had transient anginal pain with electrocardiographic ST-segment depression, but cardiac enzymes were normal.

Discussion

In this double-blind, placebo-controlled, crossover, short-term trial, oral administration of L-DOPS significantly raised BP and improved orthostatic tolerance in all patients with severe NOH attributable to PAF or MSA. The medication was well tolerated, and there were few side effects. BP rose in parallel with the increase in venous plasma NE level, but the peak increase in BP preceded the peak increase in venous plasma NE (Figure 5). This is most likely because the pressor effect depends on the level of NE at the local site of action, ie, the synaptic cleft and vascular adrenoreceptors, rather than venous plasma NE levels.

Peripherally, ie, outside the central nervous system, NE generated from L-DOPS could be stored in postganglionic sympathetic nerves and released on sympathetic activation in response to decreased baroreflex restraint during orthostasis. This is unlikely, however, because L-DOPS increased BP both in the supine and upright positions and the magnitude of increase did not change during orthostasis. Antecubital venous plasma levels of NE usually underestimate arterial plasma levels because of substantial removal of circulating NE by tissues of the forearm and hand. The peak venous plasma NE level after L-DOPS, 1250 pg/mL, probably corresponded to a substantially higher arterial plasma level. In patients with deficient baroreflex buffering of BP or denervation supersensitivity, the observed NE levels would be sufficient to increase BP. As shown in Figure 5, the threshold NE venous plasma level required to exert a pressor effect in patients with NOH was 700 pg/mL.

L-DOPS is decarboxylated to NE by the enzyme L-AADC, which is extensively expressed in neural and nonneural tissues (eg, stomach, liver, and kidney). Because L-DOPS crosses the blood-brain barrier, its pressor effect could be attributable to central activation of sympathetic outflow; however, the results of this study indicate a peripheral mechanism of action. Concomitant administration of L-DOPS with carbidopa, an inhibitor of L-AADC that does not cross the blood-brain barrier and thus inhibits NE synthesis only outside the central nervous system, blocked both the pressor effect and the increase in plasma NE.
A peripheral mechanism of action would render L-DOPS particularly effective in patients with PAF, a disorder with widespread loss of sympathetic terminals19–21 and markedly exaggerated pressor responses to infused NE.22 Consistent with this notion, the pressor response to L-DOPS in supine patients with PAF was greater than in patients with MS. Because patients with PAF have extensive loss of postganglionic sympathetic neurons, nonneural tissue, most likely stomach, liver, or kidney—where L-AADC is extensively expressed—may be the major site of NE generation from L-DOPS.16

Although precursor therapy with L-DOPS effectively treats NOH, it is not yet known whether supplementation of the depleted neurotransmitter offers additional advantages over direct agonist therapy with agents such as midodrine or pseudoephedrine, which stimulate α-adrenoreceptors. The incidence of supine hypertension, a common adverse consequence of treatment of orthostatic hypotension, was similar with L-DOPS to that in previous trials using direct adrenergic agents to treat orthostatic hypotension.23 A head to head comparison between these agents seems warranted.

Because levodopa/carbidopa therapy is a mainstay in the treatment of Parkinson disease and carbidopa inhibits conversion of L-DOPS to NE, L-DOPS may be ineffective in the treatment of NOH in such patients. In the present study, to ensure adequate L-AADC inhibition, we used a relatively high dose of carbidopa (200 mg) in combination with L-DOPS. Whether the lower doses of carbidopa, commonly used to treat Parkinson disease, also attenuate the pressor effects of L-DOPS remains unknown.

Our trial only assessed the acute effects of L-DOPS; longer trials are warranted. While taking L-DOPS, the patients were able to stand for 3 minutes significantly more often than while taking placebo. Longer orthostatic tolerance should lead to greater ability to carry out the activities of daily living and improve quality of life.

In summary, acute administration of L-DOPS increases standing BP and improves standing ability in patients with NOH attributable to degenerative autonomic disorders. The pressor effect results from conversion of L-DOPS to NE outside the central nervous system most likely in nonneuronal cells.

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