Research Article

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L-threo-dihydroxyphenylserine (L-threo-DOPS; droxidopa) in the management of neurogenic orthostatic hypotension: a multi-national, multi-center, dose-ranging study in multiple system atrophy and pure autonomic failure

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This study was designed to determine the efficacy and tolerability of increasing doses of L-threo-dihydroxyphenylserine (L-threo-DOPS) in treating symptomatic orthostatic hypotension associated with multiple system atrophy (MSA) and pure autonomic failure (PAF).

Following a one-week run-in, patients (26 MSA; 6 PAF) with symptomatic orthostatic hypotension received increasing doses of L-threo-DOPS (100, 200 and 300 mg, twice daily) in an open, dose-ranging study. Incremental dose adjustment (after weeks two and four of outpatient treatment) was based on clinical need until blood pressure (BP), and symptoms improved. Final dosage was maintained for six weeks.

With L-threo-DOPS, systolic BP decrease was reduced during orthostatic challenge (–22 ± 28 mm Hg reduction from a baseline decrease of 54.3 ± 27.7 mm Hg, p = 0.0001, n = 32; supine systolic BP at final visit was 118.9 ± 28.2 mm Hg). By the end of the study, 25 patients (78%) improved, and in 14 patients (44%) orthostatic hypotension was no longer observed. Decreased orthostatic systolic BP decrease occurred in 22% (7/32), 24% (6/25) and 61% (11/18) of patients treated with 100, 200, and 300 mg L-threo-DOPS twice daily, respectively. An improvement occurred in symptoms associated with orthostatic hypotension, such as light-headedness, dizziness (p = 0.0125), and blurred vision (p = 0.0290). L-threo-DOPS was well tolerated, with the 2 serious adverse events reported being a possible complication of the disease under study, and with no reports of supine hypertension.

In conclusion, L-threo-DOPS (100, 200, and 300 mg, twice daily) was well tolerated. The dosage of 300 mg twice daily L-threo-DOPS seemed to offer the most effective control of symptomatic orthostatic hypotension in MSA and PAF.

Key words: L-threo-DOPS, neurogenic orthostatic hypotension, multiple system atrophy (MSA; Shy-Drager syndrome), pure autonomic failure (PAF).

Orthostatic (postural) hypotension is a major disabling manifestation of autonomic failure [1]. It is associated with increased morbidity and sometimes mortality, especially in the elderly, who are at increased risk of injury due to falls [2]. Reducing orthostatic hypotension should improve patients' mobility and function, improve quality of life, and prevent falls and associated trauma [3]. The treatment of orthostatic hypotension includes nonpharmacologic and pharmacological interventions; however, the value and side effects of many of the drugs used have not been determined in appropriate clinical studies.

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L-threo-dihydroxyphenylserine (L-threo-DOPS) is an orally administered noradrenaline (NA) precursor that is metabolized to NA by L-aromatic amino acid decarboxylase. In neurogenic orthostatic hypotension (associated with noradrenergic dysfunction) L-threo-DOPS, probably through its conversion to NA and the concomitant improvement of noradrenergic function, appears beneficial [4,5]. L-threo-DOPS has been particularly successful in orthostatic hypotension due to dopamine beta hydroxylase deficiency and in some cases has been of value for over 10 years [5]. Early studies with L-threo-DOPS suggest benefit when used in the treatment of symptomatic orthostatic hypotension in patients with familial amyloidotic polyneuropathy, multiple system atrophy (MSA), pure autonomic failure (PAF) and Parkinson's disease [6–10]. The dose regimens documented in these trials ranged from starting doses of 100 mg to 200 mg L-threo-DOPS per day up to a maintenance dose of 600 mg or 900 mg daily, based on clinical need.

The dose response, safety, and tolerability of L-threo-DOPS for the treatment of orthostatic hypotension in chronic primary autonomic failure associated with MSA and PAF has not previously been determined and was the purpose of this study.

Methods

Patients

Patient inclusion criteria were: age 18 to 75 years with a diagnosis of autonomic failure related to either MSA or PAF, both symptoms (dizziness, syncope) and signs (an orthostatic decrease in systolic blood pressure (BP) of more than 20 mm Hg) of orthostatic hypotension, and written informed consent. Applicable independent ethics committee approval of the study was obtained, to cover participating centers. Patients were enrolled from centers in France (n = 5), Germany [3], and the U.K. [2].

Exclusion criteria comprised the following: idiopathic Parkinson's disease, a history (within one month before inclusion) of use or current use of any antiparkinsonian drugs except for L-dopa (alone or in combination with dopa decarboxylase inhibitors) provided that L-dopa was given at a constant dose for at least four weeks before the administration of the study drug, any need to continue proscribed concomitant medication during the period of the trial, participation in a clinical trial involving a drug under investigation within a period of two months before the start of the trial, mental disorder interfering with the diagnosis and/or with the conduct of the study (eg, schizophrenia, major depression, dementia), atrial fibrillation, serum creatinine above 130 µmol/L, any history or suspicion of barbiturate, amphetamine, or narcotics abuse or more than moderate alcohol consumption (ie, more than one liter of beer per day, or an equivalent amount of other alcoholic beverages), child-bearing potential, inability to co-operate adequately for reasons of individual or family situation, major organic disorder, and patients with known or suspected hypersensitivity to the drug.

Nonsympathomimetic therapy for postural hypotension, including salt capsules, fludrocortisone, desmopressin, and octreotide was allowed at a constant dose during the study.

Methods

Following a one-week run-in period without study medication, patients entered a (two-part) open label treatment period with dose titration of L-threo-DOPS (DOPS; Sumitomo Pharmaceuticals Co. Ltd., Osaka, Japan) from 100 mg twice daily (starting dose) to 200 mg twice daily, through to 300 mg twice daily (Figure 1). Because this was the first formal study of DOPS in white patients, part one of the study was designed to allow each investigator to make a preliminary assessment of dose response to L-threo-DOPS in an in-patient setting, thereby permitting close observation of patient response. Part one consisted of a three-day "in-patient" period with administration of L-threo-DOPS in one dose regime per day (ie, 100 mg twice daily [day one], 200 mg twice daily [day two], and 300 mg twice daily [day three]). Subject to acceptable patient response to L-threo-DOPS in part one, part two was undertaken on an outpatient basis with incremental dose adjustment after weeks two and four of treatment. Dose adjustment was made on the basis of clinical need until an improvement in blood pressure (BP), indicated by a postural decrease of less than 20 mm Hg or standing BP greater than 115/75 mm Hg), and clinical symptoms were observed. Dosage at the highest level attained was continued for a total of six weeks.

Baseline assessments of all variables described below were recorded on day one of part one, one hour before drug (first dose) intake.

The primary efficacy variable was orthostatic systolic BP decrease. Blood pressure assessments (systolic and diastolic) were carried out at the same time of day in the morning (defined in the study as two hours after morning drug intake at each visit [ie, daily in part one, and fortnightly in part two]). Orthostatic BP change was determined using four sequential measurements, after the patient had been supine for 5 and 10 minutes (before standing) and after standing for 2 and 5 minutes. Orthostatic BP decrease was defined as "the difference in the mean of systolic BP measurement after 5 minutes and after 10 minutes in a supine position minus BP measurement in a standing position." The criterion of orthostatic hypotension was fulfilled if either of the systolic BP measurements decreased by more than 20 mm Hg on

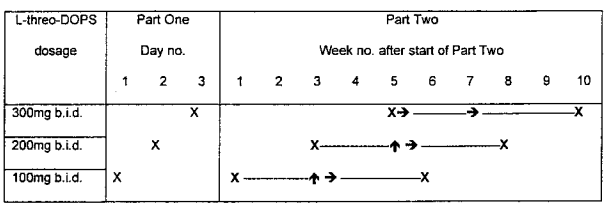

Figure 1. Dose adjustment schedule during the experimental period (all patients). Part two began immediately after day 3 of part one. ◂; ▸ = Decision point: Upward titration or maintenance at the beginning of the week indicated. A decision to adjust the dose downwards and withdraw the patient could be made at any stage.

standing, if the patient was unable to stand (from being supine) as a result of orthostatic symptoms, or if the patient fainted while standing. For any patient who fainted while standing or was unable to continue standing, BP was measured after 5 minutes of the patient's assuming a sitting position.

Plasma concentrations of noradrenaline (NA) and L-threo-DOPS were measured using high performance liquid chromatography with electrochemical detection [11,12] from 5-ml blood samples taken at each visit (before standing and after standing for 5 minutes) via an indwelling cannula inserted into the patient's forearm vein 10 minutes before blood withdrawal.

Patients completed a clinical symptoms checklist (each symptom being rated on a 10-point scale) after morning drug intake, daily (in part one) and weekly (in part two). Symptoms were rated as follows: light-headedness, dizziness (0 not at all, 10 very severe); feelings of weakness, fatigue, tiredness (0 not at all, 10 very severe); blurred vision (0 never, 10 frequently); maximal standing time (0 not at all, 10 a long time); maximal unassisted walking distance (0 not at all, 10 a long distance).

Safety measurements that included an electrocardiogram (ECG), measurement of heart rate (time-points as for the four sequential BP measurements), and routine laboratory measurements (hematology, clinical chemistry, and urinalysis), were scheduled daily in part one and at each visit in part two. Adverse event assessment was conducted throughout the trial period based on spontaneous reports from patients and in response to nonleading questions put to the patient, such as "Have you experienced any discomfort since your last visit?" and on the basis of any abnormal laboratory values.

Patient compliance in part one was assessed through investigator-witnessed in-house drug intake, and in part two with drug intake being assessed by the site staff via a check of the medication returned at each visit.

Statistical considerations

This study was designed to provide an assessment of the efficacy and tolerability of L-threo-DOPS in chronic primary autonomic failure, and the achieved sample size of 32 "efficacy-evaluable" patients was sufficient for statistical purposes, as described below. The analysis included all available data.

In cases where it was not possible to obtain measurements in the standing position, a missing data replacement policy was adopted. The method employed assigned the worst-documented outcome (ie, lowest documented standing BP value) at the respective visit, to all missing values. Such a strategy to impute missing values is an accepted one [13]. The selected method is a conservative approach and cannot be considered to favor the study hypothesis.

For orthostatic BP values, intra-group differences from baseline were tested by means of a one-sample, two-sided *t* test. Symptoms were evaluated by making a transition table, which was subjected to a Wilcoxon signed-rank test. Baseline values were calculated as the mean of values recorded at the start of run-in and at end of run-in before starting study medication.

The following correlations were tested:

(1) The change from baseline in orthostatic systolic BP decrease, versus baseline orthostatic decrease (the Spearman rank correlation coefficient).
(2) The change in orthostatic systolic BP decrease (with respect to baseline) for part one (obtained with the same dose as was reached for that patient in part two) versus part two (the Pearson correlation coefficient).
(3) The change in orthostatic systolic BP decrease (with respect to baseline) and change from baseline in clinical symptom scores (the Spearman rank correlation coefficient).

Plasma concentration data of L-threo-DOPS and noradrenaline are presented as descriptive statistics.

Data are presented as mean values ± standard deviation (SD) unless otherwise stated. A significance level of 5% was used in each statistical test, except in the case of multiple comparisons. For multiple comparisons (of orthostatic BP data) a Bonferroni correction was applied in order to control the type-I error rate. In this method, for the conducting of n significance tests, and then to get an overall type-I error rate of alpha, one would declare any one of them significant if the p value was less than alpha/n. Accordingly, in the present study (with nine individual comparisons against baseline) the result would not be declared significant unless the p value for an individual test was less than 0.0055. This is considered to be a conservative approach.

Results

Thirty-five patients were screened; of these, 2 patients failed to meet the inclusion criteria and were excluded from the trial. In total, 33 patients received L-threo-DOPS, with 1 patient discontinuing treatment because of noncompliance in part one. Of the 32 efficacy-evaluable patients, 6 were diagnosed with PAF and 26 with MSA; of the latter, 16 had the parkinsonian type, 4 the cerebellar, and 6 the "mixed" form. There were 18 males and 14 females (mean age 64.3 ± 7.1 y). The distribution in respect to age and gender among each analysis group was comparable, with the exception of gender in the PAF sub-group (1 male:5 females). Sixteen (MSA) patients received concomitant L-dopa and adjunctive dopa decarboxylase inhibitor during the study.

With L-threo-DOPS, there was a reduction in orthostatic systolic BP decrease ($p < 0.0055$ at patient final visit at a mean daily dose of 475 mg L-threo-DOPS; Fig. 2). The difference in orthostatic decrease in systolic BP from baseline to final visit after two minutes standing was −17.7 ± 34.8 mm Hg ($p = 0.0072$); baseline orthostatic BP decrease was 48.5 ± 26.9 mm Hg, and after five minutes standing −22.2 ± 28.0 mm Hg systolic BP (54.3 ± 27.7 mm Hg; $p = 0.0001$). Diastolic BP decreases on orthostatic change after L-threo-DOPS treatment were: −5.6 ± 20.5 mm Hg (19.4 ± 17 mm Hg; $p = 0.1309$) and −8.1 ± 17.2 mm Hg

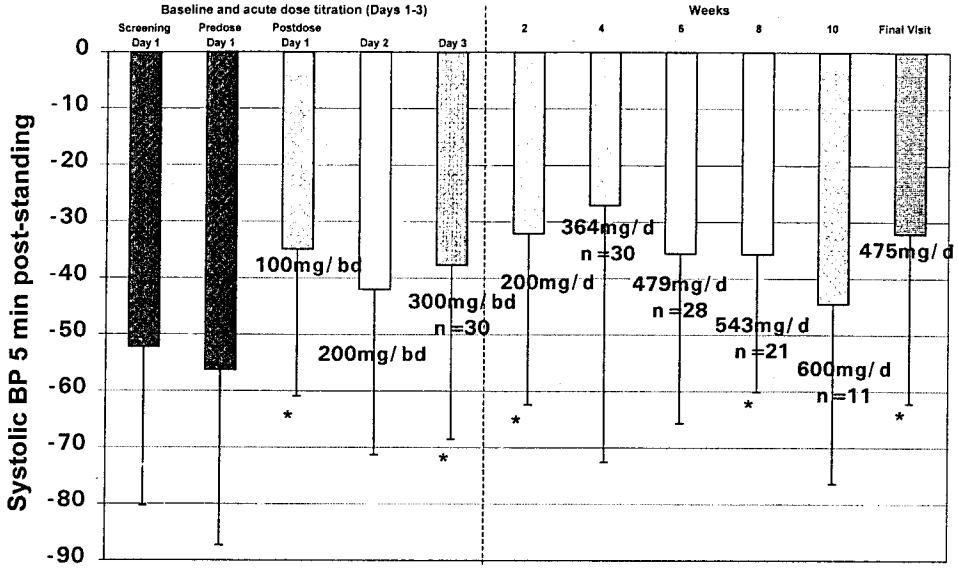

Figure 2. Orthostatic systolic blood pressure decrease at baseline and at final visit, with reference to mean daily dose of L-threo-DOPS (* = p <0.0055 versus baseline), $N = 32$ unless otherwise specified.

(24.0 ± 19.2 mm Hg; p = 0.0124) change from baseline to final visit after two and five minutes standing, respectively. Supine blood pressure at the final visit was 118.9 ± 28.2 mm Hg systolic and 70.9 ± 15.2 mm Hg diastolic.

In 25 patients (78%) there was a decrease in orthostatic hypotension (Fig. 3). In 14 (44% of the study population) of this group of 25 patients, orthostatic hypotension was no longer observed on study completion (ie, the orthostatic BP change did not exceed 20 mm Hg). No correlation between baseline orthostatic decrease in systolic BP and ameliorative effect of L-threo-DOPS on orthostatic BP decrease was observed (NS; Spearman correlation coefficients of -0.2826 and -0.3449 for orthostatic change with assessment after two and five minutes standing, respectively). Patient distribution according to the dose level attained at the final visit was, 18.8, 25, and 56.3% in the 100-, 200-, and 300-mg twice daily dose groups, respectively (Table 1).

A reduction in orthostatic systolic BP decrease occurred in 22% (7/32), 24% (6/25) and 61% (11/18) of patients treated with 100-, 200-, and 300-mg twice daily L-threo-DOPS, respectively. At final visit, a reduction in orthostatic systolic BP decrease occurred in 7/7, 6/7 and 11/18 (61%) patients receiving 100-, 200-, and 300-mg twice daily L-threo-DOPS, respectively. Change from baseline in orthostatic BP decrease after 100-, 200- and 300-mg twice daily L-threo-DOPS is presented in Table 2. A reduction in orthostatic BP decrease was observed at each dose level, though an incremental dose–effect relationship was not apparent.

No correlation was observed between the reduction in postural systolic BP decrease with respect to baseline for the initial 3-day forced-dose titration (obtained with same dose as was reached for that patient in the subsequent 6–10 week "as-needed" dose titration) and the following as-needed dose titration (obtained with "end dose") (NS.; Pearson correlation coefficient 0.4859).

Reduction in orthostatic BP decrease was comparable between PAF and MSA patient groups, and also between patients receiving L-dopa and dopa decarboxylase inhibitor versus no L-dopa and no dopa decarboxylase inhibitor as concomitant medication (Table 3).

At the final visit, light-headedness, dizziness (p = 0.0125) (Fig. 4) and blurred vision (p = 0.0290; Fig. 5) each improved compared to baseline. Overall, for the 32 efficacy-evaluable patients, none of the measured symptoms worsened.

The changes from baseline in individual symptom scores in PAF/MSA patients at last visit were: light-headedness, dizziness -2.00 (baseline value 5.00; p = 0.0625)/-1.11 (4.65; p = 0.0931); weakness, fatigue, tiredness -3.50 (7.33; p = 0.0313)/+0.30 (5.62; p = 0.8238); length of standing -2.33 (5.00; p = 0.0625)/+1.04 (5.27; p = 0.0414); walking

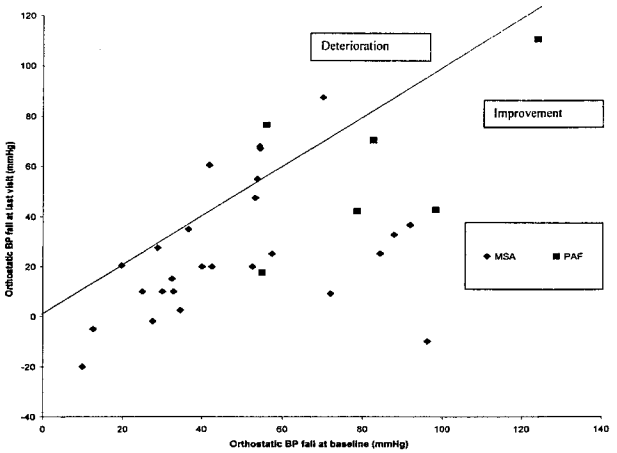

Figure 3. Orthostatic systolic blood pressure decrease at baseline and at individual last visit. Individual orthostatic blood pressure decrease (mm Hg) after 5-minutes' standing at last visit is plotted against decrease at baseline (all 32 "efficacy-evaluable" patients). Each point below the line represents a patient whose condition improved between baseline and last visit, and every point above this line a patient whose condition deteriorated. Two patients experienced an orthostatic BP decrease at baseline of less than 20 mm Hg after standing for 5 minutes, having earlier demonstrated an orthostatic BP decrease of 20 mm Hg at 2 minutes post-standing.

Table 1. End dosage

Analysis group	100 mg twice daily (*n*; %)	200 mg twice daily (*n*; %)	300 mg twice daily (*n*; %)
PAF	2 (6.3%)	0	4 (12.5%)
MSA	4 (12.5%)	8 (25.0%)	14 (43.8%)
Parkinsonian	2 (6.3%)	7 (21.9%)	7 (21.9%)
Cerebellar	2 (6.3%)	0	2 (6.3%)
Mixed type	0	1 (3.1%)	5 (15.6%)
Overall	6 (18.8%)	8 (25.0%)	18 (56.3%)

For each dosage level, the number of patients who ended the study with this dose is given.
PAF = pure autonomic failure; MSA = multiple system atrophy.

distance -1.67 (4.33; p = 0.0625)/+0.38 (6.54; p = 0.7905); blurred vision -3.67 (5.83; p = 0.0313)/-0.39 (3.50; p = 0.2632).

No correlation was found between the change in postural systolic BP decrease with respect to baseline and change from baseline in clinical symptom scores (NS; Spearman correlation coefficients ranged from -0.1039 to +0.2722).

L-threo-DOPS plasma concentration increased as the dosage was raised from 100 mg twice daily to 200 mg twice daily to 300 mg twice daily (Table 3). Plasma NA concentration (supine/end of standing period) descriptive statistics show raised resting NA levels after L-threo-DOPS (Tables 2 and 3). The data are suggestive of dose dependency between plasma concentration of NA and of L-threo-DOPS dosage. After standing, NA plasma concentrations were similar to those for prestanding/supine positions (Table 3). Plasma NA concentrations were not lower in patients on L-dopa plus dopa decarboxylase inhibitor, excluding the inhibitor's effect on reducing conversion of L-threo-DOPS.

Twenty-seven (82%) of 32 patients showed normal electrocardiograph patterns. At baseline, potentially clinically relevant deviations were observed in 4 (12%) out of 32 patients, reported as: R wave V_5 and S wave V_2 >35mm, T wave inversion, deviation in Q wave lead III, deviation in Q wave lead III and poor R wave progression. The patient with the latter pattern showed shortened QT interval (QT_c 440 msec) and a borderline ST-interval decrease (of 1.5 mm) at the third visit. The three remaining patients showed no change throughout the remainder of the study. Measured heart rates were comparable throughout the study, and there were no apparent drug- or dose-related changes. At final visit, the changes from baseline were +3.4 ± 12.9 beats/min after 10 minutes supine and +4.6 ± 13.3 beats/min after 5 minutes standing (predose baseline values were 71.3 ± 11.8 and 74.0 ± 14.5 beats/min, respectively; n = 32).

A total of 67 adverse events (AEs) were recorded for 17 patients. By dose of L-threo-DOPS, the number and incidence of AEs recorded were: 24 AEs from 13 of 33 patients who received 100 mg twice daily, 18 AEs from 8 of 25 patients who received 200 mg twice daily, and 25 AEs from 9 of 17 patients who received 300 mg twice daily. The most common adverse events were increased lactate dehydrogenase (12.1%; each event was rated as being of mild

Table 2. Dose effect of L-threo-DOPS expressed as change from baseline

	L-threo-DOPS dose		
	100 mg twice daily	200 mg twice daily	300 mg twice daily
Last individual visit per dose*	*n* = 32*	*n* = 25*	*n* = 17*
Baseline orthostatic SBP decrease	54.3 ± 27.7	55.8 ± 24.6	60.6 ± 24.9
Final visit supine SBP	120.9 ± 31.6	118.9 ± 30.3	117.2 ± 31.9
Reduction in orthostatic SBP decrease	−23.2 ± 28.0	−28.4 ± 54.4	−22.7 ± 36.4
Reduction in orthostatic DBP decrease	−9.4 ± 17.0	−10.9 ± 31.0	−11.5 ± 22.6
Noradrenaline at supine	562.5 ± 1,024.2 (*n* = 30)	779.5 ± 1,214.1 (*n* = 23)	966.1 ± 969.3 (*n* = 14)
Noradrenaline at end of standing period†	1,096.8 ± 1,228.8	1,350.1 ± 1,612.4	1,361.9 ± 864.3 (*n* = 16)
Last individual visit*	*n* = 7*	*n* = 8*	*n* = 17*
Baseline orthostatic SBP decrease	48.7 ± 38.8	45.6 ± 22.0	60.6 ± 24.9
Final visit supine SBP	129.3 ± 28.4	114.1 ± 24.6	117.1 ± 31.9
Reduction in orthostatic SBP decrease	−19.7 ± 13.9	−28.5 ± 22.2	−22.7 ± 36.4
Reduction in orthostatic DBP decrease	−9.2 ± 8.8	−5.1 ± 8.6	−11.5 ± 22.6
Noradrenaline at supine	472.1 ± 341.7	379.6 ± 394.9 (*n* = 7)	966.1 ± 969.3 (*n* = 14)
Noradrenaline at end of standing period†	1,304.6 ± 1,077.5	1,303.5 ± 1,659.8	1,361.9 ± 864.3 (*n* = 16)

Analysis used all available data, with *n* values as shown in asterisked (*) rows unless otherwise specified against mean values.
Orthostatic blood pressure decrease data were obtained after 5 min standing and are measured in mm Hg. Noradrenaline plasma concentration data are pg/ml.
†Data for noradrenaline at end of standing time represent actual values and are not presented as change from baseline.
SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 3. Plasma concentrations of noradrenaline (pg/ml) supine and standing, related to dose and plasma concentration (mcg/ml) of L-threo-DOPS, including orthostatic blood pressure data for sub-groups (expressed as change from baseline)

			NA levels (pg/ml)		L-threo-DOPS levels (mcg/ml)	
	Period	L-threo-DOPS dose	Supine	End of standing period	Supine	End of standing period
Group						
Overall	Baseline		390.8 ± 460.9 (n = 30)	421.3 ± 606.1 (n = 29)		
	Part one	100 mg twice daily	924.0 ± 1,123.1 (n = 29)	923.5 ± 825.0 (n = 30)	0.842 ± 0.389 (n = 32)	0.868 ± 0.407 (n = 32)
		200 mg twice daily	899.6 ± 839.5 (n = 32)	1,019.7 ± 753.9 (n = 31)	1.544 ± 0.761 (n = 32)	1.651 ± 0.796 (n = 31)
		300 mg twice daily	1,174.6 ± 1,225.7 (n = 30)	1,300.0 ± 1,339.3 (n = 29)	1.989 ± 0.940 (n = 30)	2.036 ± 1.052 (n = 30)
	Part two	200 mg (week 2)	883.3 ± 1,053.5 (n = 32)	1,016.1 ± 1,161.8 (n = 32)	1.004 ± 0.526 (n = 32)	1.006 ± 0.525 (n = 31)
		600 mg (week 10)	1,691.2 ± 1,169.0 (n = 9)	1,616.3 ± 913.7 (n = 10)	1.778 ± 0.796 (n = 11)	1.965 ± 0.924 (n = 11)
Subgroups					Orthostatic SBP decrease	
PAF	Predose		302.2 ± 273.0 (n = 5)	282.2 ± 198.7 (n = 5)	—	
	Part two	200 mg (week 2)	662.7 ± 299.6 (n = 6)	509.5 ± 276.2 (n = 6)	−31.5 ± 30.0 (n = 6)	
		600 mg (week 10)	1,802.0 ± 1,154.6 (n = 4)	1,728.3 ± 1,242.5 (n = 4)	−20.9 ± 32.9 (n = 4)	
MSA	Predose		408.6 ± 492.3 (n = 25)	450.3 ± 659.8 (n = 24)	—	
	Part two	200 mg (week 2)	934.8 ± 1,159.2 (n = 26)	1,114.3 ± 1,266.8 (n = 26)	−20.0 ± 28.2 (n = 26)	
		600 mg (week 10)	1,602.6 ± 1,308.1 (n = 5)	1,541.7 ± 748.2 (n = 6)	−15.5 ± 44.1 (n = 7)	
L-dopa	Predose		335.3 ± 343.5 (n = 16)	309.9 ± 138.6 (n = 15)	—	
	Part two	200 mg (week 2)	986.6 ± 1,456.4 (n = 16)	1,134.4 ± 1,592.9 (n = 16)	−17.8 ± 22.2 (n = 16)	
		600 mg (week 10)	2,527.5 ± 1,962.2 (n = 2)	2,080.0 ± 1,231.8 (n = 2)	−10.3 ± 25.6 (n = 3)	
Not receiving L-dopa	Predose		454.3 ± 574.2 (n = 14)	540.6 ± 860.8 (n = 14)	—	
	Part two	200 mg (week 2)	780.9 ± 387.3 (n = 16)	897.9 ± 471.6 (n = 16)	−26.6 ± 33.7 (n = 16)	
		600 mg (week 10)	1,452.3 ± 938.4 (n = 7)	1,500.4 ± 883.1 (n = 8)	−20.2 ± 43.9 (n = 8)	

Orthostatic blood pressure fall data were obtained after 5 min standing and are measured in mm Hg.
SBP = systolic blood pressure.

intensity and each resolved without action on the part of the investigator) and infection of the urinary tract (12.1%), followed by akinesia (9.1%), headache (9.1%), and stomach upset (9.1%). Two serious adverse events (SAEs) were recorded during the treatment period, laryngeal dyspnea and syncope at doses of L-threo-DOPS 100 mg twice daily and 300 mg twice daily, respectively. One patient's withdrawal from the study was partly attributed by the investigator to lack of efficacy, although the principal reason for withdrawal was stated as "dystonia of the right lower limb." In total, 4 patients discontinued treatment due to an adverse event, reported as dystonia, laryngeal dyspnea, lymphocytopenia (rated as being of mild intensity, 13% below the lower limit of the normal range of percentage lymphocytes), and palpitations.

Compliance in the outpatient dose–titration period was 97%.

Discussion

This study provides evidence that L-threo-DOPS reduces orthostatic hypotension and improves related symptoms in patients with chronic primary autonomic failure. While determination of the total pharmacologically mediated effect of treatment would require placebo controls, the findings are consistent with earlier placebo-controlled and double-blind investigation of L-threo-DOPS in primary autonomic failure, conducted in Japan [8]. In the present study with L-threo-DOPS, a reduction in orthostatic hypotension was observed in a high proportion (78%) of patients, with mean values showing a statistically significant reduction in BP decrease. In almost half of the study patients (n = 14) orthostatic hypotension (defined as an orthostatic decrease in systolic BP of more than 20 mm Hg) was no longer observed on study completion. The majority (18 of 32) of the

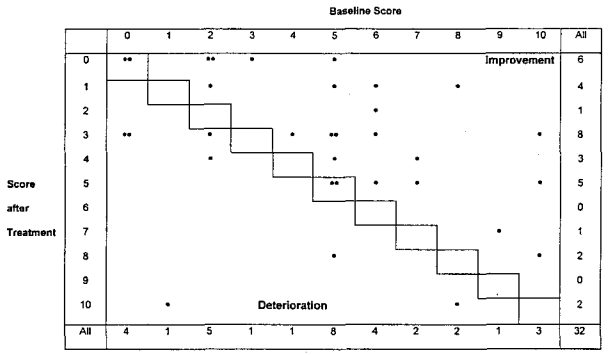

Figure 4. Transition table for the symptom "Light-headedness, Dizziness" Analysis group: Overall, N = 32. (0 = not at all, 10 = very severe). Each • represents one patient (p = 0.0125).

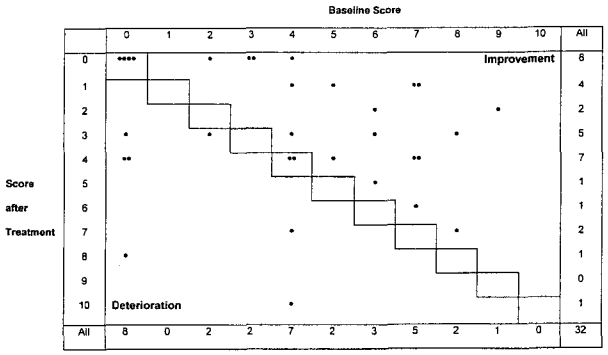

Figure 5. Transition table for the symptom "Blurred Vision" Analysis group. Overall, N = 32. (0 = not at all, 10 = very severe). Each • represents one patient (p = 0.0290).

patients were prescribed the highest dose of L-threo-DOPS (300 mg twice daily) for control of orthostatic hypotension. At this dose, a decrease in orthostatic systolic BP decrease was observed in the majority (61%) of patients; for the remaining (n = 7) patients, the orthostatic decrease in BP was not attenuated, for reasons that are unclear. The dose of 300 mg twice daily appears to be the most effective for the control of orthostatic BP decrease, given the smaller proportions of patients with reduced orthostatic BP decrease at the starting and intermediate doses of L-threo-DOPS (ie, 22% [7/32] and 24% [6/25] of those treated with 100 and 200 mg twice daily, respectively. In this study there was no apparent correlation between the reduction in orthostatic BP decrease with respect to baseline in the acute forced-titration period (such as was obtained with the same dose that was reached for that patient in the 6–10 week, as-needed titration period), raising the question of whether in practice a short-term dosage period of several days duration can assess patients' dose requirements. It seems from this study that a longer dosing schedule is required for determining such effects.

Of note were improvements in clinical symptoms of light-headedness, dizziness and blurred vision with L-threo-DOPS treatment. These symptoms commonly occur in orthostatic hypotension [3], presumably as a result of cerebral hypoperfusion, and indicate that L-threo-DOPS has the potential to improve patients' functional capacity and well being. The lack of correlation between symptomatic improvement and reduction in orthostatic decrease in systolic BP in this study emphasizes the importance of assessing both symptoms and signs. A dissociation between symptoms and signs of orthostatic hypotension has been demonstrated previously in chronic primary autonomic failure, as in the study of MSA and PAF patients where despite a 30 mm Hg orthostatic BP decrease, 5 patients did not have the usually observed symptoms of organ hypoperfusion, and had only nonspecific symptoms of lethargy, weakness and fatigue [14].

The mechanism of action of L-threo-DOPS in reducing orthostatic hypotension and its symptoms and the possibility of a differential action in the two patient groups with chronic autonomic failure under investigation warrants discussion. Plasma noradrenaline concentrations measured in peripheral venous rather than arterial blood seemed to rise with increasing dosage of L-threo-DOPS and increased plasma L-threo-DOPS concentrations, in a dose-dependent manner. In patients with MSA and PAF there is an impaired NA-response to head-up postural change, and the rise in circulating NA concentrations, especially in the presence of hypersensitivity to noradrenaline in these patients, may have been responsible for the reduction in BP decrease during orthostatic challenge. The concentrations of NA post-drug did not change appreciably on standing, raising the question of whether the beneficial response primarily was due to an increase in circulating NA and not due to recovery of sympathetic nerve function. However, increased sympathetic nerve activity, as previously reported in a single patient with MSA [15], based on sympathetic microneurography may have been responsible although this should not apply to PAF where there is evidence from both pre- and post-mortem studies of substantial postganglionic impairment, reflected also in the low basal concentrations of NA. It also may be that any change in NA or catecholamine stores in sympathetic nerve terminals, especially in patients with MSA who have relative preservation of postganglionic sympathetic pathways, was masked by higher circulating and synaptic concentrations of NA, whose precise distribution and disposition is unclear. In patients with PAF, the plasma concentrations of NA were low in comparison to those of patients with MSA, yet all PAF patients seemed to benefit to a similar degree and to a similar extent as was observed in MSA patients, therefore making it more likely that the effects were a result of the increase in plasma NA, rather than to an increase in sympathetic nerve activity.

The possible influence of concomitant L-dopa and dopa decarboxylase inhibitor on plasma NA concentrations and the response to L-threo-DOPS deserves consideration, as dopa decarboxylase inhibition may block the conversion of L-threo-DOPS to NA in the periphery and thereby affect treatment outcome. Plasma NA concentrations did not decrease as a result of concomitant dopa decarboxylase (and L-dopa) use. Moreover, an improvement in orthostatic hypotension was observed, irrespective of concomitant use of L-dopa and dopa decarboxylase inhibitor, indicating that use of such medication, as commonly used in Parkinson disease and in a number of MSA patients, is unlikely to impair the potential benefits of L-threo-DOPS, when used in conjunction with such drugs.

L-threo-DOPS was well tolerated during this study. There was no apparent relation between the frequency and nature of AEs observed and the dose level of L-threo-DOPS (100, 200, and 300 mg twice daily). The observed serious adverse events (syncope and laryngeal dyspnea) were more likely to be caused by the disease and its complications rather than by L-threo-DOPS. Syncope is an accepted feature of orthostatic hypotension because of a reduction in cerebral perfusion, whereas laryngeal stridor is a known complication in MSA, probably because of laryngeal abductor cord paresis [1,16]. Despite being a sympathomimetic, L-threo-DOPS treatment was not associated with the AEs typically associated with sympathomimetics: insomnia (ephedrine), cardiac failure (pindolol), supine hypertension (midodrine) [17], for example. These findings are consistent with previous studies in Japan of L-threo-DOPS in primary autonomic failure [8].

In conclusion, this study provided evidence that L-threo-DOPS (100, 200, and 300 mg twice daily) is well tolerated and that a dose of 300 mg twice daily offered the most effective control of symptomatic orthostatic hypotension in patients with primary autonomic failure. The positive aspects of this study merit a more detailed investigation in a larger number of patients, that will focus on appropriate dosage of L-threo-DOPS with placebo controls and clear therapeutic endpoints, to determine if L-threo-DOPS can be added to the therapeutic armamentarium in the

management of orthostatic hypotension related to primary autonomic failure.

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