

Safety and Efficacy of Northera™ (Droxidopa) for the Treatment of Symptomatic Neurogenic Orthostatic Hypotension (NOH) in Patients with Parkinson's Disease

C. J. Mathias*, MD, H. Kaufmann**, MD and the Northera Study Group

* Neurovascular and Autonomic Medicine Unit, Faculty of Medicine, Imperial College London at St Mary's Hospital

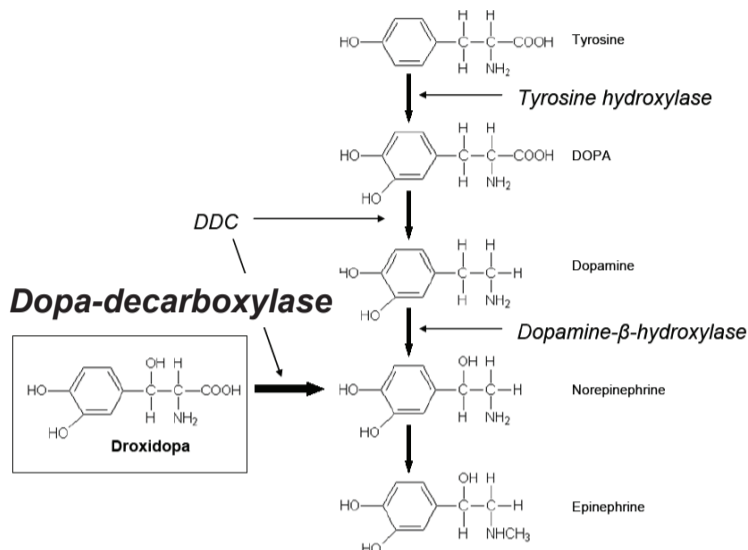
** Dysautonomia Center, New York University School of Medicine

Introduction

Typically, a drop in blood pressure upon standing is detected by baroreceptors in the walls of large arteries. This stimulates the autonomic nervous system to release norepinephrine (NE), thereby inducing vasoconstriction of arterioles and effecting a counterbalancing increase in blood pressure. However, in patients with primary autonomic failure (including pure autonomic failure (PAF), multiple system atrophy (MSA), and a subset of patients with Parkinson's disease (PD)[Kaufmann, 2002]), this homeostatic mechanism is compromised due to deficits in the production and release of NE. Thus, these patients are unable to maintain appropriate blood pressure upon standing (orthostatic hypotension, OH).

OH in these patient populations results in a number of symptoms primarily due to hypoperfusion of organs above the level of the heart, such as the brain, resulting in dizziness, visual disturbances, cognitive deficits, syncope and neck pain ("coat-hanger" pattern) [Heims, 2006; Mathias, 1999; Mathias, 2003]. OH can reduce mobility, result in falls, and may cause trauma and injuries [Rose, 2006]. Taken together, the symptomatic consequences of OH in the above patient populations can substantially reduce a patients' quality of life [Mathias, 2008; Maule, 2007; Magerkurth, 2005].

Figure 1: Synthesis of NE from Northera



Northera is an oral pro-drug that increases central and peripheral nervous system levels of norepinephrine (NE). Northera is converted to the sympathetic neurotransmitter norepinephrine (NE) through a single decarboxylation step by the endogenous enzyme 3,4-dihydrophenylalanine (DOPA) decarboxylase. Northera as an alternative precursor to norepinephrine, can provide an exogenous source of norepinephrine to adrenergic neurons that are involved in the maintenance of blood pressure.

Methods

The safety and efficacy of Northera was evaluated in a study of patients with NOH resulting from PAF, MSA and PD (N=101). We describe here results from this study for a subset of patients with NOH and PD (N=44).

The optimal dose of Northera for each patient was determined in an open-label titration protocol (100 - 600 mg t.i.d.). (see stopping rules in figure 2).

Patients continued on their optimal dose of Northera in open-label treatment for one week and were then randomized (1:1, double-blind) to receive either Northera or placebo for two additional weeks.

Figure 2: Study Design

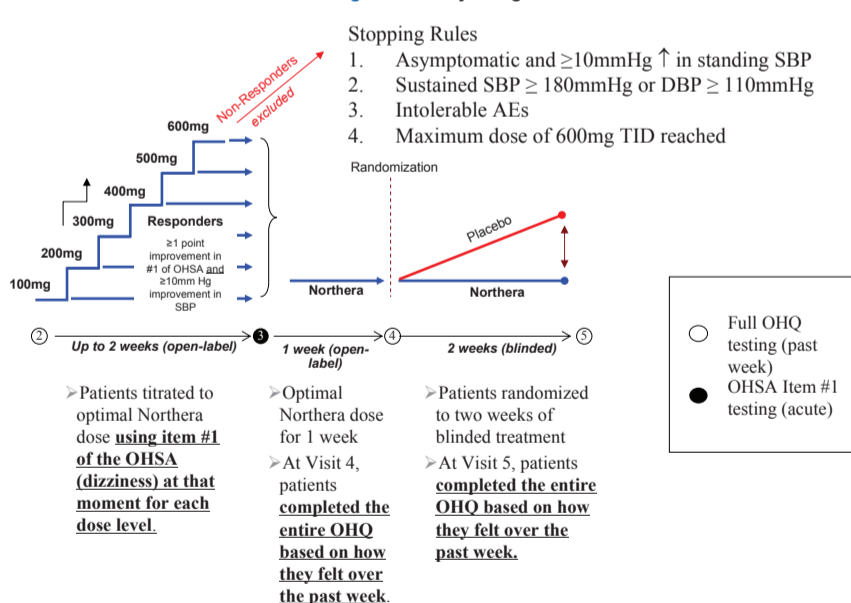


Table 1: Demographics

	PD Patients	
	Placebo	Northera
Number of Patients	23	21
Mean Age (Years)	70	72
Gender (% Male)	74	71
Mean Dose of Northera at Titration (tid)	387 mg	352 mg
DDI Use	23 (100%)	21 (100%)

Results

Figure 3

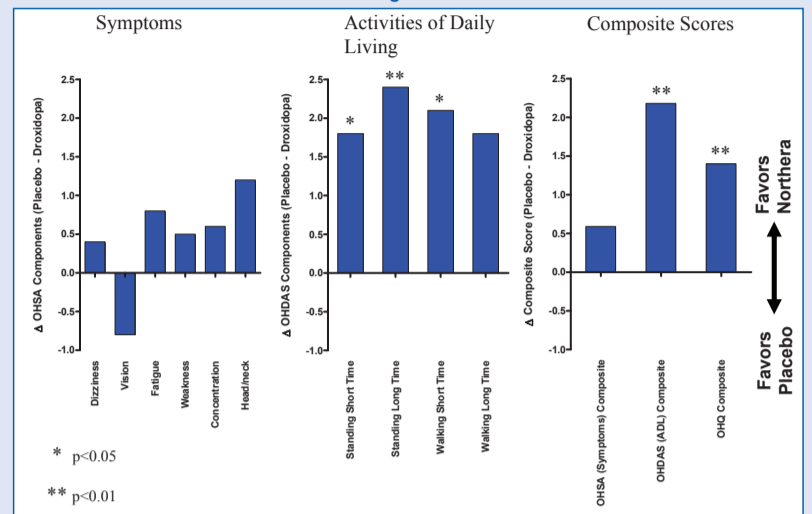


Figure 3: Changes in most measures (16/17) of signs and symptoms of orthostatic hypotension from randomization to the end of study favored Northera treated patients relative to placebo treated patients. Importantly, improvements were observed in the ability to perform activities requiring standing for a short time ($p<0.05$), standing for a long time ($p<0.01$), activities requiring walking for a short time ($p<0.05$), in the composite OHDAS ($p<0.01$) and in the composite global OHQ ($p<0.01$) scores.

Figure 4

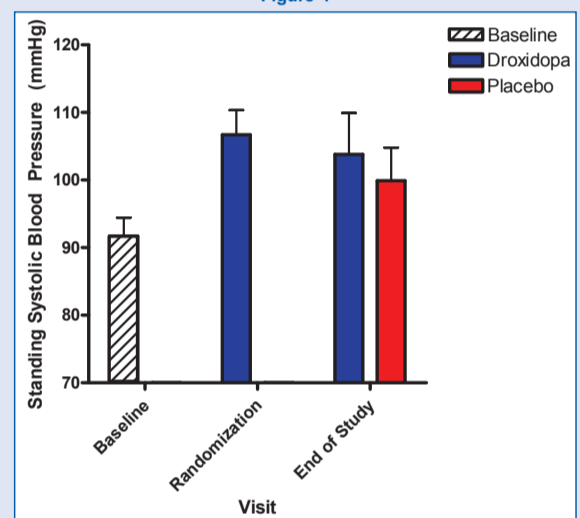


Figure 4: Standing systolic blood pressure at the end of study was elevated in the droxidopa treated group by an average of 14.7 mmHg compared with baseline.

Safety

Table 2: Overall AEs

	Placebo n=51		Northera n=50	
	# patients (# events)	%	# patients (# events)	%
SAEs	1 (2)	4	0 (0)	0
Any AEs	8 (21)	35	6 (16)	29
Relatedness				
Related	1 (1)	4	2 (2)	10
Possibly Related	2 (2)	9	2 (9)	10
Not Related	7 (18)	30	4 (5)	19
Severity				
Severe	0 (0)	0	0 (0)	0
Moderate	5 (14)	22	3 (6)	14
Mild	4 (7)	17	4 (10)	19

Table 2: Northera was not associated with an increase in the frequency or severity of adverse events relative to placebo

Conclusions

- There is evidence of substantial benefit for Northera using the composite OHQ (combined OHS and OHDAS scales) ($p<0.01$)
- There is substantial evidence of efficacy of Northera in PD patients
 - 16 of 17 outcomes with positive trends or statistically significant results
 - Significant improvement in the patients ability to perform activities of daily living as measured by the OHDAS
- Benign safety profile (adverse events comparable to those seen with placebo)
- Data from this study support previous studies that standard doses of DDI used in PD do not inhibit the effect of Northera

References

1. Heims HC, Critchley HD, Martin NH, Jager HR, Mathias CJ, et al. Cognitive functioning in orthostatic hypotension due to pure autonomic failure. *Clin Auton Res*, 2006;16 (2):113-120.
2. Kaufmann H. Treatment of patients with orthostatic hypotension and syncope. *Clin Neuropharmacol*, 2002;25 (3):133-141.
3. Magerkurth C, Schnitzer R, Braune S. Symptoms of autonomic failure in Parkinson's disease: prevalence and impact on daily life. *Clin Auton Res*, 2005;15 (2):76-82.
4. Mathias CJ, Mallipeddi R, Bleasdale-Barr K. Symptoms associated with orthostatic hypotension in pure autonomic failure and multiple system atrophy. *J Neurol*, 1999;246 (10):893-898.
5. Mathias CJ. Autonomic diseases: clinical features and laboratory evaluation. *J Neurol Neurosurg Psychiatry*, 2003;74 Suppl 3:31-41.
6. Mathias CJ. L-dihydroxyphenylserine (Northera) in the treatment of orthostatic hypotension: the European experience. *Clin Auton Res*, 2008;18 Suppl 1:25-29.
7. Maule S, Papotti G, Naso D, Magnino C, Testa E, et al. Orthostatic hypotension: evaluation and treatment. *Cardiovasc Hematol Disord Drug Targets*, 2007;7 (1):63-70.
8. Rose KM, Eigenbrodt ML, Biga RL, Couper DJ, Light KC, et al. Orthostatic hypotension predicts mortality in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Circulation*, 2006;114 (7):630-636.