Supine plasma NE predicts the pressor response to droxidopa in neurogenic orthostatic hypotension

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Abstract

Objective

To test whether the plasma levels of norepinephrine (NE) in patients with neurogenic orthostatic hypotension (nOH) predict their pressor response to droxidopa.

Methods

This was an observational study, which included patients with nOH. All patients had standardized autonomic function testing including determination of venous plasma catecholamine levels drawn through an indwelling catheter while resting supine. This was followed by a droxidopa titration with 100 mg increments in successive days until relief of symptoms, side effects, or the maximum dose of 600 mg was reached. No response was defined as an increase of <10 mm Hg in systolic blood pressure (BP) after 3-minute standing 1 hour after droxidopa administration. Nonlinear regression models were used to determine the relationship between BP response and plasma NE levels.

Results

We studied 20 patients with nOH due to Parkinson disease, pure autonomic failure, multiple system atrophy, or autoimmune autonomic neuropathies. Their supine plasma NE levels ranged from 44 to 850 pg/mL. Lower supine plasma NE levels were associated with greater pressor effect 1 hour after dose ($R^2 = 0.49$) and higher standing BP ($R^2 = 0.45$). Patients with no pressor response to droxidopa had higher NE levels (382 ± 100 vs 115 ± 20 pg/mL, $p = 0.0014$). A supine NE level of <219.5 pg/mL had 83% sensitivity and 93% specificity to predict a pressor response (area under the curve = 0.95, $p = 0.0023$).

Conclusions

In patients with nOH, lower supine resting plasma NE levels are associated with a greater pressor effect of droxidopa treatment. This finding should help identify patients with nOH most likely to respond to standard doses of droxidopa.

Classification of evidence

This study provides Class I evidence that lower supine plasma NE levels accurately identify patients with nOH more likely to have a greater pressor effect from droxidopa.

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Glossary

AAN = autoimmune autonomic neuropathy; AAG = autoimmune autonomic ganglionopathy; BP = blood pressure; MSA = multiple system atrophy; nOH = neurogenic orthostatic hypotension; NE = norepinephrine; PAF = pure autonomic failure; PD = Parkinson disease; SBP = systolic blood pressure.

Droxidopa (Northera; Lundbeck, Deerfield, IL) is a synthetic amino acid that after oral administration converts into norepinephrine (NE), the sympathetic neurotransmitter.¹ In 2014, the US Food and Drug Administration approved droxidopa for the treatment of symptomatic neurogenic orthostatic hypotension (nOH).^{1–3} However, clinical trials showed that ~30% of patients taking droxidopa had no increase in blood pressure (BP).⁴ The reason for this lack of pressor effect is unknown.

nOH can be due to lesions in the CNS or peripheral nervous systems, or due to lesions in both. Patients with nOH mainly due to CNS lesions (e.g., multiple system atrophy [MSA]) have degeneration of preganglionic sympathetic neurons but intact sympathetic fibers to the vasculature.⁵ These patients typically have normal circulating levels of NE at rest and do not develop significant adrenergic denervation supersensitivity. Their BP responses to NE are normal or only mildly increased.⁶ In contrast, patients with peripheral sympathetic lesions, such as Parkinson disease (PD), pure autonomic failure (PAF), and peripheral autonomic neuropathies, typically have reduced or absent resting sympathetic tone and low levels of circulating NE.⁷ This leads to upregulation of α -adrenergic receptors in vascular smooth muscle cells and a marked pressor response to NE or its analogs, i.e., denervation supersensitivity.⁸

We thus hypothesized that the pressor response to droxidopa in patients with nOH might depend on the extent of peripheral sympathetic neuronal loss and the degree of adrenergic denervation supersensitivity of vascular smooth muscle cells. To test this hypothesis, we measured plasma NE levels as a surrogate marker of peripheral sympathetic function in patients with central or peripheral forms of autonomic failure and evaluated their BP responses to increasing doses of droxidopa.

Methods

This was an observational study. Patients with nOH followed up at the New York University Dysautonomia Center between April 2014 and April 2018 who were clinically deemed to require droxidopa were enrolled to properly determine their dose.

Inclusion criteria were (1) patients with nOH⁹ diagnosed with standardized autonomic function testing¹⁰; (2) nOH caused by neurodegenerative synucleinopathies (PD, MSA, and PAF) according to current clinical diagnostic criteria^{7,11,12}; or (3) nOH caused by autoimmune autonomic ganglionopathies (AAGs)/autoimmune autonomic neuropathies (AANs), including AAG seropositive for antibodies against the acetylcholine ganglionic

(nicotinic) receptor,¹³ seronegative AAG defined as acute-onset nOH in combination with other signs of widespread sympathetic and parasympathetic failure such as neurogenic bladder, pupillary involvement, and gastroparesis but no identifiable serum antibodies,^{14,15} and patients with acute autonomic and sensory neuropathy.¹⁶ Patients with non-nOH, diabetes mellitus, lupus, congestive heart failure, vasovagal syncope, infectious diseases, or amyloidosis were excluded.

Standardized autonomic testing was performed in the morning after an overnight fast. Patients were asked to withhold their regular medications that morning. After the patient had remained 15 minutes of resting in the supine position, venous blood was drawn through an indwelling catheter (inserted 30 minutes before sampling) for the determination of plasma catecholamine levels.¹⁷

After nOH was confirmed, patients underwent a droxidopa titration. On the day of droxidopa administration, patients were asked to remain fasting and not to take any short-acting pressor medication (e.g., midodrine and pyridostigmine) but were allowed to take their usual fludrocortisone dose. We used a modified titration procedure similar to the one used in the droxidopa clinical trials.¹ In brief, a single dose of open-label droxidopa 100 mg was administered, and after 1 hour, BP measurements in the supine position and after 3-minute standing were taken. Droxidopa was progressively titrated in 100 mg increments in successive days until (1) complete relief of symptoms, (2) supine systolic BP (SBP) >180 mm Hg, (3) the patient experienced side effects, or (4) until the maximum dose of 600 mg was reached.

The primary outcome measure was the pressor response 1 hour after taking droxidopa defined as an increase of at least 10 mm Hg in SBP after 3-minute standing. No response was defined as an increase of <10 mm Hg in SBP after 3 minute standing 1 hour after droxidopa administration.

Statistical analysis

To determine the best cutoff value of supine plasma NE to predict which patient would have an increase in BP with droxidopa, we used receiver operating curves assuming non-parametric conditions, as previously described.¹⁸ Descriptive statistics are reported as mean $\pm$ SD unless otherwise specified. To determine whether the BP response after droxidopa had any relationship with the resting supine NE levels, a nonlinear regression model was used. We also calculated the ratio of SBP increase (mm Hg) per 100 mg of droxidopa (“response ratio” in mm Hg/mg). To determine whether this response ratio had any relationship with the resting supine NE

Table 1 Patients' demographics

Characteristic (n = 20)	
Age, years, mean ± SD	64 ± 18
Males, n (%)	13 (65)
Disease duration, ^a y, mean ± SD	6 ± 4
Diagnosis, n (%)	
PD	8 (40)
MSA	4 (20)
PAF	4 (20)
AAN/AAG	4 (20)

Abbreviations: AAG = autoimmune autonomic ganglionopathy; AAN = autoimmune autonomic neuropathy; MSA = multiple system atrophy; PAF = pure autonomic failure; PD = Parkinson disease.

^a Disease duration from onset of symptoms of neurogenic orthostatic hypotension (dizziness, lightheadedness, feeling about to faint, or syncope).

levels, all the available measurements in each patient were applied using a nonlinear regression model. $p < 0.005$ was considered statistically significant.

Standard protocol approval, registration, and patient consent

Written informed consent was obtained from all study participants. The NYU Institutional Review Board approved this study. The study was registered in ClinicalTrials.gov (NCT01799915).

Data availability statement

Anonymized data will be shared at the request of other qualified investigators for purposes of replicating procedures and results.

Results

We studied 20 patients aged 65 ± 18 years (range: 12–88 years). Sixteen patients had peripheral autonomic lesions (8 with PD, 4 with PAF, and 4 with AANs), and 4 had central autonomic lesions (MSA) (table 1). Supine plasma NE levels ranged from 44 to 850 pg/mL. The baseline BP and heart rate in the supine and 3-minute standing positions are summarized in table 2.

The final average droxidopa dose selected during titration was 320 ± 204 mg (range: 100–600 mg). The final selected droxidopa dose was 100 mg in 5 patients (2 MSA, 2 AAN, and 1 PAF), 200 mg in 5 patients (3 PAF and 2 PD), 300 mg in 3 patients (2 AAN and 1 PD), 400 mg in 1 patient with MSA, and 600 mg in 6 patients (5 PD and 1 MSA).

Both the BP in the supine position and that in the standing position after droxidopa were significantly higher compared with the baseline readings ($p < 0.001$) (table 2). Six patients, all of whom received the maximum established dose of 600 mg of droxidopa did not respond. Three patients (2 with AAN and 1 with PAF) with extremely low supine resting plasma NE levels (<90 pg/mL) experienced transient nausea/vomiting and abdominal pain and severe hypertension (SBP standing >160 mm Hg) after receiving 200 mg. Symptoms disappeared, and BP remained within acceptable limits when the dose was lowered to 100 mg.

A nonlinear regression model showed that lower plasma NE levels while supine were associated with a greater pressor effect 1 hour after dose ($R^2 = 0.49$) and a higher standing BP after the selected droxidopa dose ($R^2 = 0.45$) (figure, A). Patients who did not have a pressor response had significantly higher supine plasma NE levels (382 ± 100 pg/mL vs 115 ± 20 pg/mL, $p = 0.0014$) (figure, B). The same nonlinear model

Table 2 NE levels, blood pressure, and HR before and after droxidopa

	Before droxidopa	One hour after droxidopa	<i>p</i> Value ^a
Supine plasma NE, pg/mL, mean ± SD	195 ± 188	NA	NA
Standing plasma NE, pg/mL, mean ± SD	225 ± 202	NA	NA
Supine SBP, mm Hg, mean ± SD	128 ± 25	162 ± 22	$<0.0001^b$
Supine DBP, mm Hg, mean ± SD	72 ± 10	90 ± 11	0.0001 ^b
Supine HR, bpm, mean ± SD	71 ± 9	72 ± 17	0.896
3-minute standing SBP, mm Hg, mean ± SD	86 ± 16	113 ± 30	0.0007 ^b
3-minute standing DBP, mm Hg, mean ± SD	53 ± 14	62 ± 14	0.029 ^b
3-minute standing HR, bpm, mean ± SD	81 ± 19	80 ± 19	0.342
BP response to droxidopa, Δ mm Hg, mean ± SD	NA	+27 ± 29	NA

Abbreviations: BP = blood pressure; DBP = diastolic blood pressure; HR = heart rate; NA = not applicable; NE = norepinephrine; SBP = systolic blood pressure.

^a Paired *t* test *p* value.

^b Statistically significant differences.

also showed a good curve fit between higher SBP increase per 100 mg of droxidopa (response ratio) and lower supine plasma NE levels ($R^2 = 0.41$) (figure, C). Receiver operating curve curves showed that a supine plasma NE level of <219.5 pg/mL had 83% sensitivity and 93% specificity to predict a pressor response (area under the curve = 0.95, $p = 0.0023$) (figure, D).

Carbidopa inhibits the enzyme dopa decarboxylase, thus preventing the conversion of droxidopa to NE in a dose-dependent manner. Although our limited sample size precluded subgroup analyses, only 2 of 5 patients with PD who

did not have a pressor response to droxidopa were taking carbidopa (75 mg/d in both patients). Conversely, the 3 patients with PD who did have a good pressor response to droxidopa were receiving carbidopa (dose range: 75–225 mg/d), thus suggesting that carbidopa had no effect on the pressor response to droxidopa.

Discussion

Our results show that patients with severe widespread post-ganglionic sympathetic denervation, as reflected by supine resting venous plasma NE levels below 220 pg/mL, have the

Figure BP response and supine plasma NE levels in patients with symptomatic neurogenic orthostatic hypotension

(A) Increase in SBP after 3-minute standing 1 hour after droxidopa administration. We found a nonlinear relationship between plasma NE levels in the supine resting position and pressor response to droxidopa. (B) Plasma NE levels according to droxidopa response. Responders (those with a BP increase of at least 10 mm Hg after droxidopa administration) had significantly lower plasma NE levels in the supine resting position than nonresponders. (C) When using all the available BP response data after any droxidopa dosage in all patients, patients with higher pressor response (increase in SBP) per 100 mg of droxidopa had lower supine plasma NE levels. (D) Receiver operating curve of plasma NE levels to predict response to droxidopa. Supine plasma NE levels <219.5 pg/mL predicted with good sensitivity (83%) and excellent specificity (93%) the response to droxidopa. AUC = area under the curve; BP = blood pressure; NE = norepinephrine; SBP = systolic blood pressure.

most robust pressor response to droxidopa. Patients with less pronounced sympathetic denervation and higher supine plasma NE levels had less pressor response or failed to respond to the maximum titrated dose of 600 mg. We used a maximum droxidopa dose of 600 mg, mirroring the doses used in the droxidopa clinical trials. However, as shown before, single doses of up to 2,000 mg may be required to elicit a pressor response in some patients with nOH.¹⁹

The pathophysiology of denervation supersensitivity to NE in patients with autonomic failure is not fully understood, but increased expression of α -adrenergic receptors in vascular smooth muscle cells and lack of arterial baroreflex buffering are involved.^{8,20} Patients with neurodegenerative synucleinopathies, even with the same phenotype, have different degrees and severity of peripheral denervation. Although, in general, nOH in MSA is caused by CNS degeneration, this is not always the case, and ~30% of patients with MSA also have degeneration of peripheral sympathetic postganglionic neurons.⁵ Although our limited sample size precluded adequate subgroup analyses, it is worth noting that 2 of our patients with MSA had a pressor response to droxidopa, whereas 5 patients with PD did not. Patients with PAF and AAN, who typically have severe peripheral sympathetic denervation and low plasma NE levels, also had significant pressor responses. Thus, rather than the underlying diagnosis, it appears that the plasma NE level while in the supine position is a more sensitive and specific marker to predict the pressor response to droxidopa in patients with nOH. Further studies with adequate power to allow subgroup comparisons are required to confirm this hypothesis.

In addition to the limited sample size, our study has other limitations. NE levels were measured in forearm venous blood rather than arterial samples. The latter would have been preferable because they represent average whole-body NE concentration better.^{21–23} Cardiac sympathetic neuroimaging using ¹²³I-metaiodobenzylguanidine or ¹⁸F-dopamine can quantify myocardial denervation, which may occur in parallel to vascular sympathetic denervation and could be used in future studies to confirm our results. Future studies should include longer observation periods because patients with autonomic failure frequently have slow gastrointestinal motility, which could delay absorption of droxidopa and its pressor response.

Droxidopa converts in the body into NE, the naturally occurring sympathetic neurotransmitter, both in neural and nonneural tissue. The mechanism of the pressor effect is not fully known; it may involve the release of newly synthesized NE by sympathetic fibers into the neurovascular junction but perhaps more importantly is the effect of newly synthesized NE by nonneural tissues acting as a circulating hormone.

In patients with nOH, lower supine resting plasma NE levels are associated with a greater pressor effect of droxidopa treatment. Supine plasma NE levels <220 pg/mL have good sensitivity and specificity to predict pressor response, which is probably related to the degree of denervation supersensitivity.

Our results have clinical implications because they should help identify which patients with nOH are most likely to respond to standard doses of droxidopa.

Author contributions

J.-A. Palma: study concept and design, acquisition of data, analysis and interpretation of data, first draft of the manuscript, critical revision of the manuscript for important intellectual content, and study supervision. J. Martinez: acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. L. Norcliffe-Kaufmann: analysis and interpretation of data and critical revision of the manuscript for important intellectual content. H. Kaufmann: study concept and design, critical revision of the manuscript for important intellectual content, and study supervision.

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Disclosure

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