Short Communication

Effects of the novel norepinephrine prodrug, droxidopa, on ambulatory blood pressure in patients with neurogenic orthostatic hypotension

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Manuscript received May 17, 2016 and accepted July 18, 2016

Abstract

The prodrug droxidopa increases blood pressure (BP) in patients with neurogenic orthostatic hypotension. The BP profile of droxidopa in neurogenic orthostatic hypotension patients (n = 18) was investigated using ambulatory BP monitoring. Following dose optimization and a washout period, 24-hour “off-drug” data were collected. “On-drug” assessment was conducted after 4–5 weeks of droxidopa treatment (mean dose, 444 mg, three times daily). Ambulatory monitoring off drug revealed that 90% of patients already had abnormalities in the circadian BP profile and did not meet criteria for normal nocturnal BP dipping. On treatment, both overall mean 24-hour systolic and diastolic BPs were higher compared to off drug (137/81 mm Hg vs. 129/76 mm Hg; P = .017/.002). Mean daytime systolic BP was significantly higher with droxidopa (8.4 ± 3.1 mm Hg; P = .014). Although nocturnal BP was not significantly higher on droxidopa versus off treatment (P = .122), increases in nocturnal (supine) BP >10 mm Hg were observed in four cases (22%). Severe supine systolic hypertensive readings at night (>200 mm Hg) were captured in one case and only while on treatment. These data demonstrate that ambulatory BP monitoring is useful to evaluate the circadian BP profile after initiating treatment with a pressor agent. J Am Soc Hypertens 2016;10(10):819–826. © 2016 The Authors. Published by Elsevier Inc. on behalf of American Society of Hypertension. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Circadian rhythm; clinical trials; supine hypertension.

Introduction

Neurogenic orthostatic hypotension (nOH) is a chronic orphan condition that affects <200,000 people in the United States.1 It is caused by insufficient norepinephrine release from sympathetic nerves upon standing2 and occurs frequently in neurodegenerative synucleinopathies including Parkinson disease, dementia with Lewy bodies, pure autonomic failure, and multiple system atrophy.3,4 Failure to release norepinephrine on standing leads to defective vasoconstriction and a fall in blood pressure (BP) when upright.5,6 Symptoms occur when BP falls

Conflict of interest: H.K. is a consultant for Lundbeck NA, Ltd. L.A.H. is an employee of Lundbeck. G.J.R. was an employee of Lundbeck at the time of the analysis and manuscript development. W.B.W. is a safety consultant for Lundbeck LLC.

The data were derived from clinical trials funded by Chelsea Therapeutics, now Lundbeck LLC. L.N.-K. receives research support from the National Institutes of Health (U54NS065736) and the Dysautonomia Foundation, Inc. No author received compensation in conjunction with writing or editing of this manuscript.

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below a critical limit, and patients experience organ hypoperfusion, with cardinal symptoms including disabling lightheadedness or syncope.7

Droxidopa (L-threo-3,4-dihydroxyphenylserine) is a synthetic amino acid that is converted to norepinephrine by the ubiquitous enzyme, dopa-decarboxylase.1,8 Clinical trials show that oral administration of droxidopa produces a pressor response that lasts for approximately 6 hours.6,9 The BP response is associated with an improvement in symptoms of nOH in patients with synucleinopathies and chronic autonomic failure.10–12 Droxidopa is approved in the United States for the treatment of patients with symptomatic nOH.

During clinical trials, the impact of droxidopa on BP was assessed using BP measurements acquired during an office visit. However, in patients with nOH, office BP readings do not fully characterize the circadian variation of BP.13 In clinical practice, ambulatory BP monitoring is often used to evaluate the response to treatment with pressor agents throughout a typical day.13 In addition to capturing BP variations while awake, it can also be used to assess nocturnal BP, which is often elevated in patients with synucleinopathies and autonomic failure. Supine hypertension is often worsened by the very therapies used to treat daytime orthostatic hypotension.14,15 which creates a difficult clinical conundrum.

Here, we examined the ambulatory BP profiles in patients with symptomatic nOH associated with synucleinopathies on droxidopa and compared these values to those following a washout period off drug.

Methods

Study Design

The ambulatory BP study was conducted as a component of a multicenter, randomized trial of droxidopa and open-label extension studies in individuals with nOH as a result of autonomic failure.14,16,17 The protocol was approved by the site-specific institutional review boards, and written informed consent was obtained for all participants. Procedures were performed in accordance with the standards of the Declaration of Helsinki. All data were deidentified.

Subjects were recruited for this substudy from those individuals participating in a randomized controlled trial of droxidopa11 and who were intending to participate in the open-label extension trials.16,17 Subjects were screened for eligibility, and suitable candidates were enrolled in an open-label dose optimization titration phase of the randomized double-blind, placebo-controlled 1-week clinical trial (Figure 1). Following the dose optimization phase, subjects underwent a washout period for a minimum of 2 days, and then, an ambulatory BP recording was obtained (off-drug reading).

Upon completion of the randomized clinical trial, participants resumed their optimal droxidopa dose in the open-label extension studies. After a minimum of 4 weeks of open-label treatment, an ambulatory BP recording was obtained.

Inclusion and Exclusion Criteria

To be eligible for inclusion in the study, patients had to be older than 18 years and have a clinical diagnosis of nOH due to Parkinson disease, pure autonomic failure, multiple system atrophy, or autonomic neuropathy. nOH was defined as a documented decrease of $\geq 20$ mm Hg systolic BP or $\geq 10$ mm Hg diastolic BP within 3 minutes of standing. Key exclusion criteria included nOH as a result of diabetes, use of pressor agents such as midodrine, sustained severe hypertension ($\geq 180/110$ mm Hg while seated), and clinically significant renal, hepatic, or cardiac disease.

Droxidopa Administration

In the parent randomized controlled trial, dosing of droxidopa was initiated at 100 mg three times daily (TID) and was adjusted upward at subsequent visits until the participant met any one of the following stopping criteria: (1) complete resolution of symptoms, (2) reached the maximum dose of 600 mg TID, (3) development of sustained hypertension ($\geq 180/110$ mm Hg in any position),
or (4) intolerable side effects. The optimal dose was defined as the dose at which criteria 1 or 2 were achieved or the dose level below which criteria 3 or 4 were met. Following identification of the optimal dose, patients underwent a washout period (a minimum of 2 days to a maximum of 5 days); 24-hour “off-drug” data were collected following the washout period. The minimum 2-day washout was determined from the known 2- to 3-hour plasma half-life of droxidopa. Patients were then treated with their optimal dose of droxidopa for 4 to 5 weeks, and an “on-drug” ambulatory assessment was conducted at the end of this period. Droxidopa was administered in oral doses TID, which were divided into three equal doses every 4 hours during the daytime. To avoid worsening of supine hypertension at night, patients were verbally instructed to take their last dose of droxidopa no later than 4 hours before going to bed. Patients were told to sleep with the head of the bed elevated at a 30-degree angle.

**BP Monitoring**

Ambulatory BP was recorded using a validated monitor (Model 90,207; SpaceLabs Medical, Inc; Issaquah WA, USA), which was programmed to measure BP at 30-minute intervals over a 24-hour period. The appropriate

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### Table 1
Characteristics of the patients at baseline

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, y</th>
<th>Sex</th>
<th>Underlying Diagnosis</th>
<th>Supine SBP/DBP, mm Hg</th>
<th>Standing* SBP/DBP, mm Hg</th>
<th>Supine Heart Rate, bpm</th>
<th>Standing* Heart Rate, bpm</th>
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<td>76</td>
<td>M</td>
<td>PAF</td>
<td>130/78</td>
<td>78/30</td>
<td>109</td>
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<tr>
<td>2</td>
<td>66</td>
<td>M</td>
<td>PAF</td>
<td>174/92</td>
<td>113/83</td>
<td>74</td>
<td>74</td>
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<tr>
<td>3</td>
<td>75</td>
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<td>F</td>
<td>PD</td>
<td>124/72</td>
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<td>6</td>
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<td>74</td>
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<td>61</td>
<td>M</td>
<td>PD</td>
<td>118/75</td>
<td>83/55</td>
<td>84</td>
<td>100</td>
</tr>
</tbody>
</table>

Mean ± SEM 74 ± 6

BP, blood pressure; SEM, standard error of the mean.

* After 3 minutes.

† Error value reported as SD.

‡ n = 17.

### Table 2
Mean ± SEM ambulatory blood pressures and heart rates off and on treatment with droxidopa in patients with neurogenic orthostatic hypotension (n = 18)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No Treatment</th>
<th>Droxidopa</th>
<th>Change From off Treatment to On Treatment</th>
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</thead>
<tbody>
<tr>
<td>Ambulatory systolic BP, mm Hg</td>
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<td></td>
<td></td>
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<tr>
<td>24 hour</td>
<td>129 ± 3</td>
<td>137 ± 3</td>
<td>7.3 ± 2.8*</td>
</tr>
<tr>
<td>Daytime†</td>
<td>123 ± 2</td>
<td>131 ± 3</td>
<td>8.4 ± 3.1*</td>
</tr>
<tr>
<td>Nighttime‡</td>
<td>136 ± 5</td>
<td>143 ± 6</td>
<td>7.8 ± 4.8</td>
</tr>
<tr>
<td>Ambulatory diastolic BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hour</td>
<td>76 ± 2</td>
<td>81 ± 2</td>
<td>4.8 ± 1.3†</td>
</tr>
<tr>
<td>Daytime†</td>
<td>74 ± 2</td>
<td>79 ± 2</td>
<td>5.5 ± 1.8*</td>
</tr>
<tr>
<td>Nighttime‡</td>
<td>78 ± 4</td>
<td>83 ± 3</td>
<td>4.8 ± 2.5</td>
</tr>
<tr>
<td>Ambulatory heart rate, beats/min</td>
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<tr>
<td>24-hour</td>
<td>74 ± 1</td>
<td>76 ± 1</td>
<td>+2.0 ± 0.8</td>
</tr>
<tr>
<td>Daytime*</td>
<td>77 ± 2</td>
<td>79 ± 1</td>
<td>+2.1 ± 1.4</td>
</tr>
<tr>
<td>Nighttime*</td>
<td>71 ± 2</td>
<td>72 ± 2</td>
<td>+0.5 ± 0.9</td>
</tr>
</tbody>
</table>

BP, blood pressure; SEM, standard error of the mean.

* P < .05.

† 8 AM–4 PM.

‡ 11 PM–5 AM.

§ P < .01 vs. off treatment; Wilcoxon signed-rank test.
cuff sizes were determined by midarm circumference and were fitted to the nondominant arm, as described previously. Quality criteria for an acceptable ambulatory BP recording included a minimum of 80% valid readings obtained within 24 hours after monitor hookup, and no more than 2 consecutive hours or 5 nonconsecutive hours without a valid reading. Quality of the recordings was reviewed, and if these criteria were not met, ambulatory recordings were repeated one more time. If quality criteria were not met after repeating the recording, data were deemed unsatisfactory and excluded from the analysis. Blinded ambulatory BP data were transmitted to and reviewed by a single source (Integrium Cardiovascular Core Laboratory, Tustin, CA).

Analyses

The primary objective of the study was to compare mean 24-hour systolic BP at baseline (following drug washout) with measurements taken after 4 weeks of droxidopa treatment. Secondary end points included the changes in mean systolic BP during the daytime (defined as 8 AM–4 PM, when patients were assumed to be awake and physically active) and nighttime (defined as 11 PM–5 AM, when patients would be most likely to be in bed and in the supine position). Variables examined included the presence of nocturnal dipping (defined as a 10% or greater reduction in systolic BP during the night compared with the day) and the incidence of varying levels of stage 2 hypertension, defined as systolic BP values of ≥160, ≥180, and ≥200 mm Hg. No efficacy evaluations were included in this substudy, and all other safety variables (beyond BP effects) are reported as part of the parent study (randomized controlled trial or open-label extension trials).

Statistical Analyses

Comparisons between baseline values and values after droxidopa treatment were examined using the Wilcoxon signed-rank test and 95% confidence intervals (CIs) based on paired t tests. The incidence of hypertension was determined by the proportions of patients at baseline and on treatment with various BP values at night assessed using chi-square and Fisher exact tests. The incidence of hypotension was determined by the proportion of patients with daytime systolic BP readings ≤80 and ≤70 mm Hg. Statistical significance was set at P < .05.

Results

Patients

A total of 20 patients participated in the ambulatory BP substudy at eight sites. Two patients were excluded from the analysis because their ambulatory recordings did not meet quality criteria. Hence, complete data at baseline and on treatment were available for 18 patients. The baseline characteristics of the participants are shown in Table 1. The mean ± standard deviation age of the cohort was 74 ± 6 years, the majority of patients (72%, 13/18) were male, and 100% of patients were white. Two-thirds of the patients (12/18) had a diagnosis of Parkinson disease.

At baseline (off treatment), the mean ± standard error of the mean clinical BP readings in the supine position
were 130/77 mm Hg. Mean standing BP readings were 88/58 mm Hg, with an average fall of 41/17 mm Hg. After baseline assessments and completion of the randomized clinical trial, patients entered the open-label extension study and were treated with an individually optimized dose of droxidopa (mean standard deviation, 444 mg TID; range, 100 mg–600 mg).

24-Hour Ambulatory BP

At the end of the washout period, the off-drug mean 24-hour BP was 129/76 ± 2 mm Hg (Table 2). After 4 weeks of droxidopa treatment, the mean 24-hour systolic BP increased by 7.3 ± 2.8 mm Hg (P = .017; 95% CI, 1.5–13.1 mm Hg; Figure 2A) and mean diastolic BP increased by 4.8 ± 1.3 mm Hg (P = .002; 95% CI, 2.0–7.7 mm Hg). The resultant mean 24-hour BP was significantly higher than off drug (137/81 ± 3/2 mm Hg; P < .017).

Daytime BP

During the off-drug period, the mean daytime (8 AM–4 PM) systolic BP was 123 ± 2 mm Hg (Table 2). Off treatment, 22% of patients (4/18) had individual systolic readings <80 mm Hg and 11% (2/18) had individual readings <70 mm Hg. As shown in Figures 2B and 3, on-treatment mean ± standard error of the mean daytime systolic BP readings were significantly increased by 8.4 ± 3.1 mm Hg (P = .014; 95% CI, 1.9–14.9 mm Hg). On treatment, 11% of patients (2/18) had systolic readings <80 mm Hg and 1 patient had values <70 mm Hg.

Nighttime BP

Mean systolic BP during the night (11 PM–5 AM) was significantly higher than during the day at baseline (136 ± 5 mm Hg vs. 123 ± 2, respectively; P = .02). Only two patients (both with primary autonomic failure)
had a 10% or greater fall in BP at night. The remaining 90% of patients (16/18) had circadian BP abnormalities with either blunted dipping (a <10% fall in night vs. day) or reversal of the normal circadian rhythm and higher values at night (a \( \geq 10\% \) increase in systolic BP at night vs. day; 45% [8/18] for each).

In patients receiving droxidopa therapy, mean systolic BPs were numerically (7.8 ± 4.8 mm Hg) but not significantly higher at night compared to the off-treatment period \( (P = .122; \text{Figures 2C and 3}). \) Similar to the baseline period, mean systolic BPs were higher at night (143 ± 6 mm Hg) compared with those during the day (131 ± 3 mm Hg; \( P < .017 \)). Seven patients (39%) had a \( \geq 10\text{-}10\text{ mm Hg increase in nocturnal systolic BP with treatment with droxidopa compared with baseline. Four patients (22\%) had average nocturnal systolic BP values \( \geq 160 \text{ mm Hg}\); 2 of these patients (11\%) had systolic BP values \( > 180 \text{ mm Hg}, \) and no patients had average systolic BP values \( > 200 \text{ mm Hg}. \) Moreover, there were similar proportions of participants with nighttime systolic BP readings greater than \( \geq 160, \geq 180, \) or \( \geq 200 \text{ mm Hg at baseline and on treatment (Table 3).} \)

**Discussion**

This study is the first to examine the effects of droxidopa on ambulatory BP in a group of patients with well-defined synucleinopathies. Oral administration of droxidopa significantly increased mean BP during the day \( (+8.4 \text{ mm Hg}; P = .014) \), with nonsignificant increases during the night \( (+7.8 \text{ mm Hg}; P = .121). \) There have been theoretical concerns that nocturnal BP on droxidopa would be higher than those measured during the day because patients would more likely be supine. However, only a small subset of patients (2/18, 11\%) developed clinically important hypertension at night (mean nocturnal systolic BP \( \geq 180 \text{ mm Hg}\) during droxidopa treatment versus not on treatment. The implications of nocturnal hypertension in patients with autonomic failure are of clinical importance. Elevated nocturnal BP with supine hypertension is associated with progression of end-organ target damage and is predictive of cardiovascular events, including stroke. \( \text{14,19,21–23} \) Hence, our findings underscore the importance of nighttime BP measurements in patients with nOH because baseline nocturnal BP abnormalities are common and might be further exacerbated by treatment with pressor agents. This preliminary study appears to indicate extreme effects are unlikely in most patients. When ambulatory BP monitoring is performed, it is essential to note carefully the timing of pressor agent doses as well as an accurate timing of sleep. This information is critical to interpreting the effects of a pressor agent on the circadian BP profile.
Our findings also emphasize the importance of taking the last daily dose of droxidopa (or any pressor agent) several hours before retiring for the night, allowing enough time for the vasoconstrictor effect to diminish. Developing a higher nocturnal BP on treatment with droxidopa does not necessarily indicate that the agent should be discontinued or that the risks would be lessened by switching to an alternative pressor agent. There are no direct comparisons of droxidopa versus other pressor agents (e.g., midodrine), and it is not known how other pressor agents affect nighttime BP; to the best of our knowledge, ambulatory BP studies evaluating these effects have not been published. However, because these agents increase systemic vasoconstriction, they are all likely to carry the risk of raising nocturnal BP if taken too close to bedtime. Patients with nOH should sleep with the head of the bed elevated.24,25 Such a simple maneuver reduces venous return and lowers BP at night (while supine). Based on the available data with droxidopa, reduction or elimination of the last dose of the day may be considered if the patient has supine hypertension and raising the head of the bed and/or a short-acting antihypertensives are not adequate for BP control.

Blunted nocturnal dipping is associated with increased cardiovascular risk.26,27 Patients with nOH have an increased incidence of blunting of the normal nocturnal dipping pattern. There are currently no established clinical care guidelines for the management of high supine BP during the night in patients with autonomic failure. Short-acting antihypertensive agents at night may be useful,28 including calcium antagonists and angiotensin-converting enzyme inhibitors; however, an agent of choice has not emerged, and the potential problems of worsening hypotension when patients get out of bed during the night must be carefully considered.

An obvious limitation of the study is the small number of patients. Further studies examining ambulatory BP monitoring in a larger cohort are needed to confirm these findings.

In conclusion, the results of the present study provide evidence that droxidopa, a norepinephrine replacement therapy, leads to increases in ambulatory BP during the day with an acceptably low risk (estimated to be 10% to 20%) of increasing supine hypertension at night. Ambulatory BP monitoring may help to identify the minority of patients who do develop nocturnal supine hypertension.

Acknowledgments

The authors received editorial assistance from Lisa M. Havran, PhD, CHC Group (North Wales, PA), which was supported by Lundbeck, LLC. All authors, as well as the funding body, participated in the design, conduct, and analysis of this study, reviewed the final manuscript, and agreed with the decision to publish.

References

14. Vagaonescu TD, Saadia D, Tuhrim S, Phillips RA, Kaufmann H. Hypertensive cardiovascular damage in...