Cardiovascular Safety of Droxidopa in Patients With Symptomatic Neurogenic Orthostatic Hypotension

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The norepinephrine prodrug droxidopa improves symptoms of neurogenic orthostatic hypotension, a condition that is associated with diseases of neurogenic autonomic failure (e.g., Parkinson disease, multiple system atrophy, pure autonomic failure). These conditions are more prevalent in older patients who also have cardiovascular co-morbidities. Hence, we evaluated the cardiovascular safety of droxidopa in patients with symptomatic neurogenic orthostatic hypotension who participated in randomized controlled studies (short-term studies of 1 to 2 weeks and an intermediate 8- to 10-week study) and long-term open-label studies. Rates of cardiovascular adverse events (AEs) for patients treated with droxidopa were 4.4% in the intermediate study and 10.8% in the long-term open-label studies. Adjusting for exposure time, cardiovascular AE rates were 0.30 events/patient-year in the short-term and intermediate studies and 0.15 events/patient-year in the long-term open-label studies. The incidence of treatment discontinuation due to blood pressure−related events was approximately 2.5%. Among patients with a history of cardiac disorders at baseline, the rates of cardiovascular-related and blood pressure−related AEs were nominally higher with droxidopa compared to placebo. Most of these events were minor atrial arrhythmias; none were major adverse cardiovascular events or deaths. In conclusion, small increases in cardiovascular AEs were observed with droxidopa compared to placebo; this was most evident in patients with preexisting cardiac disorders. **(Am J Cardiol 2017;119:1111−1115)**

Neurogenic orthostatic hypotension (nOH) is caused by loss of the noradrenergic baroreceptor reflex, which can arise from dysfunction of central autonomic pathways or peripheral autonomic fibers caused by primary autonomic failure or other neuropathic conditions.[1] These neurogenic syndromes are associated with excessive cardiovascular (CV) morbidity and may also result in an increased risk of falls and related injuries.[2] Droxidopa, a synthetic oral prodrug of norepinephrine, is a novel therapy for symptomatic nOH caused by autonomic failure syndromes.[3−6] In randomized, double-blind, placebo-controlled phase 3 trials of patients with nOH, droxidopa decreased nOH symptoms (dizziness, lightheadedness, feeling faint) and reduced the fall rate.[7] CV co-morbidities are common in patients with nOH,[8,9] and droxidopa increases norepinephrine levels and has the potential to increase supine blood pressure (BP).[9,10] Even without treatment for orthostatic hypotension, approximately 50% of patients with nOH with primary autonomic failure have supine hypertension,[11,12] which can be associated with left ventricular hypertrophy or increased nocturnal pressure natriuresis.[13−15] Hence, we evaluated the CV safety of droxidopa in patients with symptomatic nOH who participated in controlled clinical trials and in the long-term open-label extension program of the drug.

Methods

The CV safety of droxidopa was examined in an analysis of CV- and BP-related adverse events (AEs) reported in the phase 3 clinical development program for this orphan therapy. Data were derived from 3 randomized, placebo-controlled trials[3−6] and 2 long-term open-label studies[16,17] and were grouped according to study design and treatment duration (short-term, intermediate [8 to 10 weeks] double-blind, or long-term open-label; Figure 1). The design of the 2 short-term pivotal studies[3,6] approved (and advocated) by the US Food and Drug Administration identified patients who responded to open-label titration of droxidopa before randomization of these responders to 1 or 2 weeks of double-blind, placebo-controlled treatment. In the intermediate double-blind study,[4,5] patients with Parkinson disease were randomized to dose titration of placebo or droxidopa followed by 8 weeks of stable dosing. In the 2 long-term studies,[16,17] mean exposure to droxidopa was 312 days (maximum exposure, 714 days) and 362 days (maximum exposure, 1,133 days), respectively. Doses of droxidopa used in the studies were titrated to effect and tolerability and ranged from 100 to 600 mg thrice daily. Duration of drug exposure was defined as the number of days from the first to the last dose of study drug (droxidopa or placebo) taken by the patient.

All studies included adults diagnosed with symptomatic nOH, confirmed by a documented decrease of $\geq$20 mm Hg in

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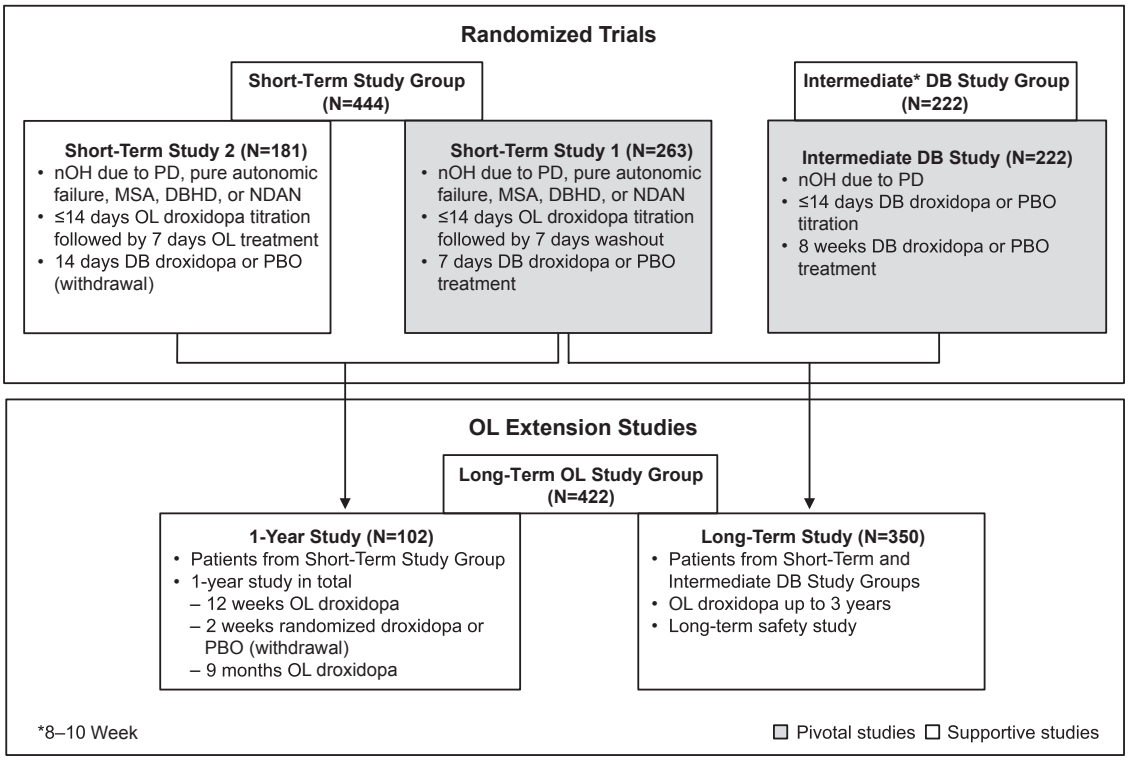

Figure 1. Patient flow and study groupings for analyses. DB = double-blind; DBHD = dopamine β-hydroxylase deficiency; MSA = multiple system atrophy; NDAN = nondiabetic autonomic neuropathy; OL = open-label; PBO = placebo; PD = Parkinson disease.

systolic BP or ≥10 mm Hg in diastolic BP within 3 minutes after standing. Patients eligible for enrollment in the short-term and long-term studies had nOH associated with primary autonomic failure (Parkinson disease, multiple system atrophy, and pure autonomic failure), dopamine β-hydroxylase deficiency, or nondiabetic autonomic neuropathy, whereas patients eligible for enrollment in the intermediate double-blind study had nOH associated with Parkinson disease only. Patients in the long-term studies were required to have participated in one of the short-term studies or the intermediate double-blind study. Patients completing the 1-year long-term study[16] were also eligible to continue open-label droxidopa treatment in a separate long-term study.[17]

Exclusion criteria for the studies were preexisting sustained severe hypertension (BP ≥180/110 mm Hg in the sitting position), clinically significant cardiac arrhythmias, myocardial infarction, current unstable angina, or uncompensated congestive heart failure (New York Heart Association Class III or IV). Vasoconstrictor agents or long-acting antihypertensive therapies were not allowed. Use of serotonin-norepinephrine reuptake inhibitors was excluded in all studies except the intermediate double-blind study.

CV AEs occurring during treatment and serious AEs were identified using the system organ classes and preferred terms of the *Medical Dictionary for Regulatory Activities* (Supplementary Table 1). There was no formal CV adjudication process during droxidopa development. If a patient experienced multiple events that mapped to a single preferred term, the greatest severity was assigned for the applicable table. BP events included those classified as hypertension, hypertensive crisis, and increased BP. In the long-term open-label studies, terms of malignant hypertension and BP fluctuations were also recorded based on the information provided by the patients' physicians. The incidence rates of CV events were determined in the subgroups of patients with or without baseline CV conditions in the short-term and intermediate double-blind studies. Baseline CV conditions included arrhythmias, ischemic heart disease, hypertension, ventricular hypertrophy or cardiomegaly, aortic stenosis, valvular abnormalities, and congestive heart failure.

Twelve-lead electrocardiograms were performed during double-blind treatment in the short-term studies, at baseline and during stable dosing in the intermediate double-blind study, and at each study visit in the long-term open-label studies. The electrocardiograms were evaluated for heart rate and QT, RR, PR, and QRS intervals. QT intervals were corrected for heart rate using Bazett's formula (QTcB) and Fridericia's formula (QTcF). The electrocardiogram parameters were tabulated by visit and by the frequency of QTcB or QTcF intervals ≥450, ≥480, and ≥500 ms. Changes from baseline in QTcB or QTcF were also categorized as ≥30 and ≥60 ms.

CV- and BP-related AEs and electrocardiogram results in each study grouping were combined for analysis. AE incidence was adjusted for exposure to study drug expressed in events per patient-year. AEs that were treatment emergent, serious, and that led to treatment discontinuation were tabulated. Data were summarized using descriptive statistics.

Results

The baseline characteristics of the patients in the various studies are provided in Table 1. Parkinson disease was the primary diagnosis for about 40% of patients in the short-term study group, all patients in the intermediate