Prospects for Droxidopa in Neurogenic Orthostatic Hypotension

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Neurogenic orthostatic hypotension (nOH) is a debilitating disorder defined by a sustained decrease in systolic blood pressure of 20 mm Hg or in diastolic blood pressure of 10 mm Hg within 3 minutes of head-up tilt or standing. The disorder is associated with attenuated increases in plasma norepinephrine and peripheral resistance upon orthostasis as well as the absence of baroreflex-mediated tachycardia, which are reflective of impaired sympathetic and parasympathetic reflexes to modulate blood pressure.2 Recently, droxidopa, a synthetic precursor of norepinephrine, was approved for the treatment of nOH; however, the efficacy of the drug in long-term trials was unclear.

In this issue of Hypertension, Biaggioni et al1 investigated the effects of droxidopa in patients with nOH, who were previously responsive to the drug, with a month-long, double-blind, placebo-controlled withdrawal study. The main finding of the study was that patients randomized to continue droxidopa had similar reports of lightheadedness compared with patients who were randomized to the placebo; orthostatic blood pressure was also similar between groups. These findings could suggest that a placebo effect occurred or that droxidopa was not washout in some patients ≤2 weeks after cessation. Yet, the group who continued to receive droxidopa experienced significantly greater improvement in self-rated health, ability to stand, and many symptoms of nOH (weakness, fatigue, trouble concentrating, and head/neck discomfort). These conflicting data raise the important question of what should be considered successful treatment of nOH; should subjective improvement of symptoms and perceived health be the main goal of treatment rather than orthostatic blood pressure or reports of lightheadedness? Moving forward, further studies investigating the effects of droxidopa in nOH should define the primary study outcome to equate with a broader range of symptomatic and physiological improvement and the withdrawal period should be >2 weeks to address the potential carryover effect and examine long-term efficacy of droxidopa in responding patients.

In addition, it will be interesting to see how droxidopa compares with other treatments, in particular midodrine, the only other Food and Drug Administration–approved drug for nOH. The α1 adrenergic receptor agonist, midodrine, has shown to improve orthostatic blood pressure in nOH, but trials to access symptomatic improvement are currently underway. Most concerning about midodrine is the side effect of supine hypertension, which commonly presents in patients with nOH before the initiation of treatment. However, droxidopa also produces supine hypertension and timing of drug administration will be key, although it is unclear whether droxidopa will be a safer alternative to midodrine.

Although droxidopa is a produg converted to norepinephrine, which can also activate α1 adrenergic receptors, the actions of norepinephrine are not limited to that target. As shown in the Figure, droxidopa could potentially have numerous physiological effects that may ameliorate or exacerbate symptoms of nOH. One mechanism of action is that droxidopa is endocytosed by postganglionic peripheral sympathetic neurons, converted to norepinephrine, and released when the neuron depolarizes.3 This process expectedly targets innervated α1 adrenergic receptors to enhance vasoconstriction. However, droxidopa can also be converted to norepinephrine and further to epinephrine in the adrenal medulla and then released into circulation. These circulating catecholamines can activate a range of adrenergic receptors including α1 receptors to enhance vasoconstriction, α2 receptors to inhibit norepinephrine release from nerve terminals, and β-adrenergic receptors to increase vasodilation and heart rate. Also unlike midodrine, droxidopa is able to cross the blood–brain barrier and possibly enhance norepinephrine production in the central nervous system, which could have either beneficial or deleterious effects in patients with nOH. Although possible targets for droxidopa in the brain and spinal cord have not been investigated, the most probable effector would be the locus coeruleus, the main noradrenergic nucleus in the brain. The locus coeruleus is involved in numerous pathways relating to arousal, cognition, and autonomic control that span the cortex, hypothalamus, brainstem, and spinal cord.5 However, the potential effects of droxidopa on central nervous system pathways and their relation to symptomatic improvement in nOH are unknown.

It will also be important to access which groups of patients will benefit most from droxidopa. It is likely that certain patients with nOH will have more to gain from this drug than others. In particular, those with the rare dopamine β-hydroxylase deficiency may benefit from droxidopa most because they are unable to synthesize norepinephrine naturally and acute trials have demonstrated improvement in symptoms and orthostatic blood pressure in this subset of patients.7 Patients with...
autonomic neuropathies may also benefit more from droxidopa because increased concentration of circulating catecholamines may enhance activation of adrenergic receptors on blood vessels that are denervated. Yet, patients with diabetes mellitus, one of the most common causes of neuropathy, have been excluded from most trials. Droxidopa certainly holds promise for the long-term treatment of nOH, but the advantage of this drug over other treatments and which subsets of patients will benefit most from droxidopa are yet to be determined.

Disclosures

None.

References

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