Cognitive and Behavioral Changes in Patients Treated With Droxidopa for Neurogenic Orthostatic Hypotension: A Retrospective Review

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Abstract

Background: Droxidopa is a norepinephrine precursor that improves symptoms of neurogenic orthostatic hypotension in conditions such as Parkinson disease, multiple system atrophy, and pure autonomic failure by inducing a pressor effect. Unlike other pressor agents, droxidopa crosses the blood-brain barrier; however, its central effects are, as of yet, uncharacterized.

Objective: We present the results of a retrospective cohort study examining cognitive and behavioral side effects linked to droxidopa therapy.

Methods: We performed a review of 101 patients who had been treated with droxidopa at an academic tertiary care center and identified cases of cognitive and behavioral changes associated with the therapy.

Results: We identified six patients who had developed cognitive and behavioral symptoms, including memory difficulties, confusion, mania, and irritability, shortly after droxidopa initiation. All six patients displayed symptoms of synucleinopathy, manifesting with autonomic failure, rapid eye movement sleep behavior disorder, and parkinsonism. Patients had no significant cognitive or behavioral symptoms before droxidopa initiation. Behavioral disturbances were observed early in the droxidopa titration period and at relatively low doses. Symptoms resolved with dose reduction in four patients, and droxidopa was discontinued in two patients due to persistent irritability. No other medical comorbidities or alternative etiologies were identified to explain the symptoms.

Conclusions: Droxidopa is designed to act peripherally as a pressor agent but may also exert important central effects. We hypothesize that the cognitive and behavioral manifestations observed in the patients with orthostatic hypotension resulted from an "overdose" of key noradrenergic networks linking orbitofrontal and mesolimbic regions.

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Keywords

norepinephrine; droxidopa; Parkinson disease; neurogenic orthostatic hypotension; cognition; behavior

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Droxidopa is a norepinephrine precursor that has been approved for the treatment of neurogenic orthostatic hypotension in conditions such as Parkinson disease (PD), multiple system atrophy, and pure autonomic failure. Droxidopa became the second medication to receive approval from the US Food and Drug Administration for the treatment of neurogenic orthostatic hypotension in 2014, following the approval of midodrine in 1996 (Kaufmann et al, 2015). The mechanism of action of droxidopa is somewhat unique: It is a prodrug that is converted to norepinephrine by l-aromatic amino acid decarboxylase. Droxidopa is postulated to exert its effect on peripheral blood pressure through three possible mechanisms: (a) by peripheral conversion to norepinephrine, which then acts as a circulating vasoconstrictor hormone, (b) by conversion to norepinephrine within sympathetic nerve terminals and subsequent release as a neurotransmitter, and (c) by crossing the blood-brain barrier and acting as a central stimulator of sympathetic outflow (Kaufmann et al, 2015).

In initial studies, droxidopa was shown to improve patient-reported symptoms of neurogenic orthostatic hypotension over a 2-week period, with the most commonly reported adverse events including headache, dizziness, nausea, and hypertension (Biaggioni et al, 2015; Kaufmann et al, 2014). Thus far, clinical studies have focused solely on droxidopa's peripheral effects, although droxidopa may also have effects on central noradrenergic networks that are as of yet uncharacterized. One study indicated a nonsignificant trend toward improvement in fatigue and trouble concentrating on droxidopa therapy (Biaggioni et al, 2015), and another preliminary study reported a reduction in falls in patients with PD who had been treated with droxidopa as compared with placebo (Hauser et al, 2014). Moreover, two early studies from Japan suggested that treatment with droxidopa improved freezing of gait (Narabayashi et al, 1984; Tohgi et al, 1993).

Whether droxidopa influences central noradrenergic activity, and, if so, what the potential symptomatic consequences may be, is currently unknown. We present the results of a retrospective cohort study reviewing our experience with droxidopa at Vanderbilt Medical Center over the last 4 years. Within this time period, six patients were identified who developed adverse cognitive and behavioral symptoms associated with the initiation of droxidopa therapy. These findings suggest that droxidopa may, in fact, modulate central noradrenergic networks, which could have important therapeutic implications. We hypothesized that the cognitive and behavioral manifestations may result from an "overdose" of key noradrenergic networks linking the orbitofrontal and mesolimbic regions of the brain.

METHODS

We performed a retrospective review of patients who had been treated with droxidopa at Vanderbilt Medical Center, an academic tertiary care center in Nashville, Tennessee, between November 2014 and January 2018. Based on pharmacy records, we identified 101

patients who initiated droxidopa therapy during this time period. We then performed a comprehensive chart review for each patient, including analysis of droxidopa titration schedule and dosing, medical comorbidities, clinical course, and outcome. We screened all patient records for any potential adverse events following droxidopa initiation, and we flagged all reports of cognitive or behavioral symptoms (eg, memory difficulties, confusion, mania, irritability, agitation, or disorientation) for further review.

Inclusion criteria for this cohort included the development of any new cognitive or behavioral symptoms, either during the titration period or within 1 month of reaching the target dose of droxidopa, that subsequently resolved with dose reduction or discontinuation. Exclusion criteria were significant preexisting cognitive impairment, comorbid psychiatric or behavioral symptoms, and an unclear time line or relationship to droxidopa initiation. The study was approved by the Vanderbilt Medical Center Institutional Review Board.

RESULTS

We identified six patients who developed cognitive and behavioral symptoms, including mania, irritability, and disorientation, shortly after the initiation of droxidopa for neurogenic orthostatic hypotension. Four patients were male and two were female, aged 59 years to 82 years. All of the patients had symptoms of synucleinopathy, including autonomic failure, rapid eye movement sleep behavior disorder (RBD), and parkinsonism. Five of the patients met the clinical criteria for idiopathic PD, and one was diagnosed with possible autoimmune autonomic neuropathy but also had concomitant symptoms of parkinsonism and RBD. All six patients had symptomatic orthostatic hypotension, with an average decrease in blood pressure upon standing of 29mmHg systolic and 11mmHg diastolic.

All six patients included in our study underwent in-clinic cognitive or neuropsychological testing before the initiation of droxidopa. Each patient exhibited some degree of mild cognitive symptoms, as would be expected in a PD population, including deficits in executive function, memory, and attention; however, none of the six patients met the criteria for dementia. Five of the six patients also had comorbid depression and anxiety, as is common in this population. None of the patients had previously experienced any acute behavioral symptoms similar to those that developed after the initiation of droxidopa.

Patient 1

A 58-year-old man with idiopathic PD was started on droxidopa for symptomatic orthostatic hypotension. Dosing was initiated at 100mg twice a day (BID) and was titrated up to 400mg three times a day (TID) over 4 weeks. After 5 days at this dosage, the patient developed confusion, agitation, fear, and manic symptoms. Droxidopa was stopped for a week and the symptoms resolved. The patient subsequently resumed droxidopa 200mg BID and reported feeling more alert, without any adverse effects. Concomitant medications included ropinirole XL 4mg daily, entacapone 200mg TID, and carbidopa-levodopa 25–100mg two tablets four times a day and three tablets every night at bedtime.

Patient 2

An 82-year-old woman with idiopathic PD was started on droxidopa 100mg BID for symptomatic orthostatic hypotension with a planned up-titration to 300mg BID over 4 days. However, after the dose was increased to 200mg BID, the patient reported confusion, fatigue, and dizziness. When the dose was increased to 300mg BID, the patient's confusion worsened. Her family reported that she got lost in her own house and appeared manic and agitated, "rambling around all over." She could not sleep and wandered through the house all night. Droxidopa was stopped, and the symptoms resolved within 24 hours. A few days later, the patient resumed droxidopa at 100mg BID, which she tolerated well. Fludrocortisone was subsequently added for continued severe orthostatic hypotension. Concomitant medications included carbidopa-levodopa 25–100mg seven tablets daily, sertraline 100mg daily, and rivastigmine 9.5mg daily.

Patient 3

A 67-year-old woman with idiopathic PD was started on droxidopa 100mg BID for symptomatic orthostatic hypotension, with a planned up-titration to 400mg BID. At 200mg BID, the patient noticed increased anxiety but improved energy and blood pressure stability. After her dose was increased to 400mg BID, she complained of confusion and memory problems, which improved when the dose was decreased back to 200mg BID. The patient was subsequently able to continue on this dose and noticed an improvement in her fatigue and energy level. Concomitant medications included carbidopa-levodopa 25–100mg two tablets four times a day, carbidopa-levodopa extended release 25–100mg two tablets at bedtime, paroxetine 40mg daily, and clonazepam 0.5mg at bedtime.

Patient 4

A 74-year-old man with idiopathic PD was started on droxidopa 100mg TID and was gradually titrated up to 600mg four times a day due to severe orthostatic hypotension. Shortly after reaching the maximum dose, he developed irritability, anxiety, and perseveration. Droxidopa was stopped and restarted at 300mg BID, but he again developed irritability and argumentativeness, following which droxidopa was stopped. Two months later, the patient was restarted on droxidopa 100mg TID by a local neurologist. When his dose was increased to 300mg TID, the patient again developed irritability and aggressive behavior, which did not resolve with a decreased dose to 200mg TID. Droxidopa was subsequently discontinued. Concomitant medications included carbidopa-levodopa 25–250mg six and a half tablets daily, entacapone 200mg five times daily, fludrocortisone 0.1mg BID, midodrine 2.5mg TID, pyridostimine 30mg TID, rivastigmine 4.6mg daily, and melatonin 3mg at bedtime.

Patient 5

A 72-year-old man with autonomic failure, RBD, and parkinsonism was started on droxidopa 100mg BID and was titrated up to 200mg BID after 48 hours. Shortly after reaching this dose, he developed hypertension of up to 200 mmHg systolic and 100 mmHg diastolic (when sitting), along with significant irritability and memory difficulties. His wife reported that he also experienced increased anxiety and frustration as well as anger outbursts

toward his family that were "very uncharacteristic of him." His dose was then decreased to 200mg every morning and 100mg every evening, with resultant improvement in his blood pressure and irritability. He was not on any other dopaminergic or noradrenergic medications. At a return visit, the patient was noted to have fatigue, weight loss, and lymphadenopathy, due to which he was diagnosed with lymphoma. Acetylcholine receptor ganglionic antibodies were negative, but his presentation was assessed to be suspicious for autoimmune autonomic neuropathy; thus, he was treated with rituximab and plasmapheresis. He continues on droxidopa 200mg every morning and 100mg every evening for orthostatic hypotension.

Patient 6

A 59-year-old man with diffuse Lewy body disease was started on droxidopa 100mg BID and was titrated up to 400mg BID over a 2-week period for orthostatic hypotension refractory to fludrocortisone. He subsequently developed agitation and irritability and reported that the medication was "making me crazy." He self-discontinued droxidopa and fludrocortisone 6 months later, and his symptoms resolved. He has since remained off medication for his orthostatic hypotension and has noted some lightheadedness upon standing, which was resolved by rising from a seated position slowly. Concomitant medications included carbidopa-levodopa 25–100mg one and a half tablets TID, carbidopa 25mg TID, carbidopa-levodopa extended release 50–200mg at bedtime, entacapone 200mg TID, and venlafaxine 150mg extended release daily.

Table 1 provides a summary of the presented cases.

DISCUSSION

This cohort of patients presenting with prominent cognitive and behavioral changes closely associated with droxidopa initiation suggests that droxidopa may not only act peripherally but may also have important effects on central noradrenergic networks. In the initial randomized controlled trials leading to the approval of droxidopa, the most common adverse events reported were headache, dizziness, nausea, and hypertension (Biaggioni et al, 2015; Kaufmann et al, 2014). No adverse cognitive or behavioral effects were reported in these studies, although no formal cognitive assessments were conducted. However, both of these trials did include the Orthostatic Hypotension Symptom Assessment (Kaufmann et al, 2012) as a secondary endpoint, which contains questions about fatigue and trouble concentrating. The Kaufmann et al trial (2014) showed no change in trouble concentrating on droxidopa but did find a nonsignificant trend toward improvement in fatigue. The Biaggioni et al trial (2015) showed a trend toward improvement in both fatigue and concentration with droxidopa; however, neither effect was statistically significant. Finally, in a recent long-term, open-label safety study involving 350 patients with symptomatic neurogenic orthostatic hypotension, the most commonly reported adverse events were falls (23.4%), urinary tract infections (13.4%), headaches (12.0%), syncope (12.0%), and dizziness (9.7%) (Isaacson et al, 2016). However, no cognitive or behavioral side effects were reported.

To our knowledge, ours is the first report of adverse cognitive and behavioral effects attributed to droxidopa therapy prescribed for neurogenic orthostatic hypotension.

Behavioral disturbances in the patients were observed early in the titration period and at relatively low doses of droxidopa (total daily doses ranging from 300mg/day to 800mg/day, compared to the maximal recommended dose of 1800 mg/day). Symptoms resolved with dose reduction in four patients, and droxidopa was discontinued in two patients due to persistent symptoms.

All of the patients in our cohort had symptoms of an underlying synucleinopathy, including autonomic failure, RBD, and parkinsonism. Five of the patients met the criteria for idiopathic PD, and one had autonomic failure associated with parkinsonism and RBD. No other medical comorbidities or alternative etiologies were identified to explain the symptoms, although it is important to consider the potential role of concomitant medications in predisposing patients to these effects. Five of the six patients were concurrently taking carbidopa, a dopa decarboxylase inhibitor that can increase the amount of droxidopa available to the blood-brain barrier. Furthermore, three patients were taking a catechol-O-methyl transferase inhibitor, and one was concurrently on a norepinephrine reuptake inhibitor as well, all of which may potentiate the central effects of droxidopa.

This study has several important limitations. Because this was a retrospective review, the patients were not asked about cognitive and/or behavioral symptoms in a systematic way, and the symptoms only came to medical attention if they were volunteered by patients or caregivers at a follow-up visit. Likewise, follow-up for these patients was not standardized. All of the patients included in the cohort were seen at least once in a follow-up period after droxidopa initiation, but other appointments not at our center may have been missed. Finally, the sample size for this study was relatively small, as these symptoms were only observed in six out of 101 cases reviewed. Further studies of larger cohorts are needed to elucidate potentially differential effects across a wider range of underlying diagnoses, involving different degrees of both peripheral and central noradrenergic activity, including PD, multiple system atrophy, and pure autonomic failure.

We hypothesize that these cognitive and behavioral manifestations may result from an "overdose" of key noradrenergic networks linking the orbitofrontal and mesolimbic regions of the brain (Figure 1). Noradrenergic neurons are located in the locus coeruleus and have widespread projections to the frontal and prefrontal cortices, basal forebrain, limbic system, thalamus, and cerebellum. Norepinephrine plays a key role in cognitive functions, including attention, working memory, and alertness, and noradrenergic therapies are widely used in conditions such as depression and attention deficit hyperactivity disorder (Borodovitsyna et al, 2017). However, evidence suggests that excessive noradrenergic activation can be detrimental. For example, elevated levels of norepinephrine in plasma and cerebrospinal fluid have been associated with symptoms such as paranoia in schizophrenia (Borodovitsyna et al, 2017), and increased extracellular norepinephrine and activation of noradrenergic receptors have been linked to the manic phase of bipolar disorder (van Enkhuizen et al, 2015). Furthermore, similar symptoms of mania and irritability have previously been reported in patients with attention deficit hyperactivity disorder treated with the norepinephrine reuptake inhibitor, atomoxetine (Bahali et al, 2013; Guney and Uneri, 2014; Henderson and Hartman, 2004), and medication-induced psychosis has been associated with stimulants such as methylphenidate (Kraemer et al, 2010; Rafiq and Shah, 2013; Strattera,

2002). This evidence corroborates our findings and suggests that the symptoms observed in our patients are attributable to increased central norepinephrine levels induced by droxidopa therapy. Clinicians prescribing droxidopa should, therefore, be attuned to the potential behavioral side effects associated with its use.

Although the adverse effects we observed suggest that droxidopa may have a negative impact in some patients, these findings may present an opportunity for others. While this study focused on adverse cognitive and behavioral effects, it is important to note that five patients (out of the initial 101 reviewed) reported significant improvements in their energy levels on droxidopa, and four reported improvement in gait and a reduction in falls. These findings suggest that droxidopa may in fact modulate central noradrenergic activity in a beneficial way for some patients, which could have therapeutic implications for conditions such as PD, which is associated with central norepinephrine deficiency (Braak et al, 2003; Del Tredici and Braak, 2013; Goldstein et al, 2012; Hurst et al, 1985).

In conclusion, the results of this retrospective cohort study suggest that droxidopa therapy for orthostatic hypotension may be associated with cognitive and behavioral changes in some patients. These symptoms suggest that droxidopa may cross the blood-brain barrier and modulate central noradrenergic networks in addition to its intended peripheral activity. Further studies are warranted to better characterize potential central noradrenergic effects in patients treated with droxidopa.

Acknowledgments

Glossary

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BID	twice a day
PD	Parkinson disease
RBD	rapid eye movement sleep behavior disorder
TID	three times a day

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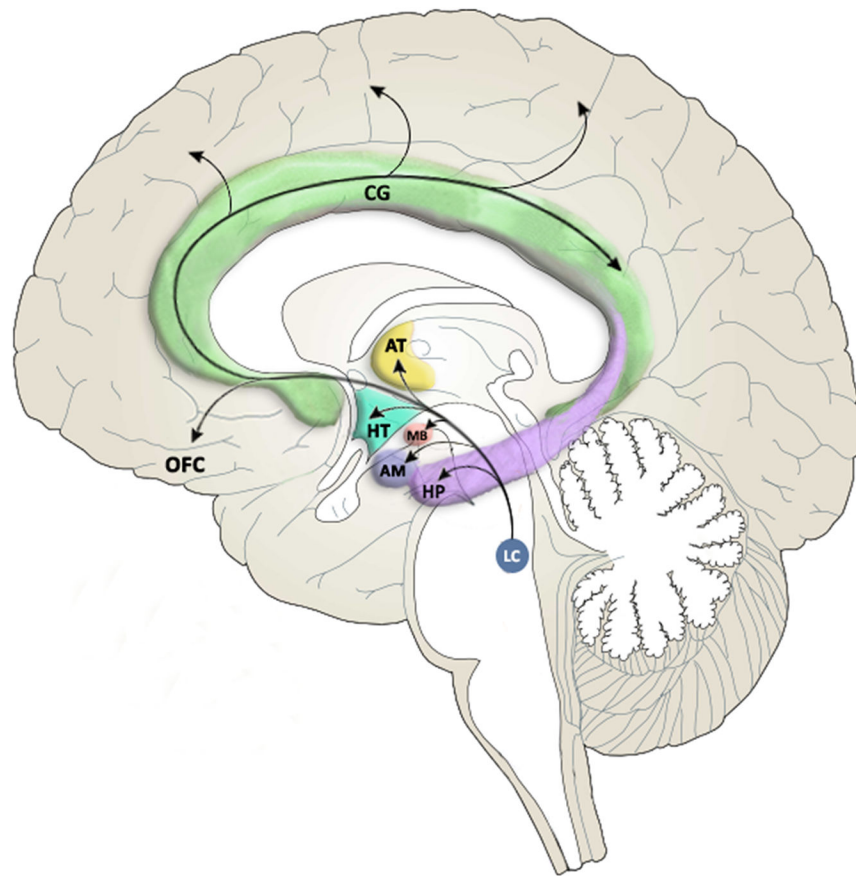
FIGURE 1.
Noradrenergic innervation of the orbitofrontal and limbic regions of the brain. (Figure 1 can be viewed in color online at www.cogbehavneurol.com.)

AM = amygdala. **AT** = anterior thalamus. **CG** = cingulate gyrus. **HP** = hippocampus. **HT** = hypothalamus. **LC** = locus coeruleus. **MB** = mammillary body. **OFC** = orbitofrontal cortex.

TABLE 1.

Droxidopa Treatment for Six Patients With Neurogenic Orthostatic Hypotension

Patient	Age	Sex	Diagnosis	Symptoms	Droxidopa Dose	Outcome
1	58	M	PD	Confusion, agitation, fear, mania	400mg TID	Resolved at 200mg BID
2	82	F	PD	Confusion, fatigue, dizziness, mania, rambling speech, wandering, agitation	300mg BID	Resolved at 100mg BID
3	67	F	PD	Anxiety, memory difficulties	400mg BID	Resolved at 200mg BID
4	74	M	PD	Irritability, anxiety, perseveration, aggressive behavior	300mg BID	Discontinued
5	72	M	PAF, RBD, parkinsonism	Irritability, anxiety, memory difficulties, anger outbursts	200mg BID	Resolved at 200mg every morning and 100mg every evening
6	59	M	Diffuse Lewy body disease	Agitation, irritability	400mg BID	Discontinued

BID = twice a day. **F** = female. **M** = male. **PAF** = primary autonomic failure. **PD** = Parkinson disease. **RBD** = rapid eye movement sleep behavior disorder. **TID** = three times a day.