Droxidopa for Hypotension of Different Etiologies: Two Case Reports

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ABSTRACT

Orthostatic hypotension is defined as a decrease in systolic blood pressure of at least 20 mmHg or a decrease in diastolic blood pressure of at least 10 mmHg (or both), within three minutes of moving from a supine to an upright or standing position. Droxidopa is a synthetic amino acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, subsequently providing alpha and beta-agonist effects to increase blood pressure. It is indicated in the treatment of neurogenic orthostatic hypotension caused by primary autonomic failure that is associated with Parkinson disease, multi-system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, and/or non-diabetic autonomic neuropathy. In addition, it has been studied in other disease states, such as diabetic autonomic neuropathy-associated orthostatic hypotension and supine hypotension. We report on two cases of off-label droxidopa use. The first case was for diabetic autonomic neuropathy-associated orthostatic hypotension, and the second case was for hypotension due to autonomic dysfunction associated with rheumatoid arthritis. Although the outcomes differed in each case, this article contributes to the literature demonstrating that droxidopa may have varying effects in treating orthostatic hypotension of non-neurogenic etiology.

Keywords: droxidopa, diabetic autonomic neuropathy, orthostatic hypotension, autonomic dysfunction, rheumatoid arthritis

INTRODUCTION

Orthostatic hypotension is defined as a decrease in systolic blood pressure (SBP) of at least 20 mmHg or a decrease in diastolic blood pressure (DBP) of at least 10 mmHg (or both), within three minutes of moving from a supine to an upright position.[1] It can be brought on by the decrease in baroreceptor sensitivity as a result of aging, volume depletion, autonomic failure, neurodegenerative disease, and/or medications. In its most severe form, orthostatic hypotension can cause large decreases in BP leading to syncopal episodes.[2]

Droxidopa (Northera, Lundbeck) is a synthetic amino-acid analog that is directly metabolized to norepinephrine by dopa-decarboxylase, subsequently providing alpha and beta-agonist effects to induce peripheral, arterial, and venous vasoconstriction, which ultimately increases BP. In clinical trials, it has demonstrated efficacy in the treatment of neurogenic orthostatic hypotension (nOH), which is caused by primary autonomic failure associated with Parkinson disease (PD), multiple system atrophy, pure autonomic failure, dopamine beta-hydroxylase deficiency, or non-diabetic autonomic neuropathy.[3] The recommended starting dose of droxidopa is 100 mg orally (PO) three times daily (TID), and it can be titrated up to 600 mg TID. Doses can be altered per symptomatic response every 24 to 48 hours.[3-4] Droxidopa has a half-life of approximately 2.5 hours, is 26–75% protein-bound, and is primarily excreted through the urine.[3]

The following are two cases of off-label use of droxidopa: the first was for diabetic autonomic neuropathy and the second was for autonomic dysfunction related to rheumatoid arthritis (RA).

CASE 1

A 69-year-old Caucasian male presented to the hospital following a syncopal episode, during which he hit his head. His medical history was significant for orthostatic hypotension with previous syncopal episodes, congestive heart failure, myocardial infarction, atrial fibrillation, ventricular tachycardia (after which he had an implantable cardioverter defibrillator placed), bioprosthetic aortic valve replacement, chronic obstructive pulmonary disease, anemia, hyperlipidemia, chronic kidney disease, gout, type-2 diabetes mellitus (T2DM), peripheral neuropathy, myalgia, diverticulosis, and gastroesophageal reflux. His home medications included allopurinol (Zyloprim®), apixaban (Eliquis®), aspirin, atorvastatin (Lipitor®), chlorthalidone (Thalitone®), docusate (Colace®), eplerenone (Inspra®), escitalopram (Lexapro®), gabapentin (Neurontin®), insulin regular (Humulin R®), isosorbide mononitrate (Imdur®), liraglutide (Victoza®), meloxicam (Mobic®), metolazone (Zaroxolyn®), metoprolol (Lopressor®), midodrine (Proamatine®) 5 mg TID, pantoprazole (Protonix®), potassium chloride, torsemide (Demadex®), and umeclidinium-vilanterol inhaler (Anoro Ellipta®). Except for midodrine, medication dosages were not available. His allergies included possible upper airway edema with penicillin and shortness of breath with iodinated contrast media.

In the emergency department (ED), the patient's initial BP was 91/51 mmHg, his heart rate (HR) was 82 beats per minute (bpm), his respiratory rate (RR) was 18 breaths per minute, and his oxygen saturation (SpO_2) was 99% on room air. His only complaint at that time was anxiety. He was administered one liter (L) of normal saline over one hour. Approximately 30 minutes later, his BP increased to 95/62 mmHg. The following home medications were held: chlorthalidone, eplerenone, isosorbide mononitrate, metolazone, and metoprolol. A computed

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tomography (CT) head scan showed no acute changes, and a cervical spine CT scan showed no dislocations or fractures.

The patient tested positive for orthostatic hypotension, with a BP of 87/46 mmHg while sitting, and 61/29 mmHg upon standing three minutes later. Pertinent laboratory data are listed in Table 1. A blood urea nitrogen/serum creatinine (BUN/SCr) ratio of 19:2 indicated intrinsic renal disease. All other laboratory parameters were within normal limits. Skin turgor and mucous membranes also were within normal limits. A trace of edema was noted in the lower extremities. Upon auscultation, diminished lung sounds were noted in the lower lobes. The electrocardiogram (ECG) showed normal sinus rhythm (NSR). The patient's transthoracic echocardiogram showed moderate concentric left-ventricular hypertrophy with a left-ventricular ejection fraction of 35–40% and hemodynamically insignificant aortic stenosis.

On day 2 of admission, droxidopa 100 mg PO TID and fludrocortisone 0.1 mg PO were initiated. No further orthostatic tests were conducted. Four days later, the droxidopa dose was increased to 200 mg PO TID (see Figure 1) to improve the patient's BP response. He received triple therapy, including midodrine, for four days. Upon discharge, midodrine was discontinued and he was continued on droxidopa 200 mg TID and fludrocortisone 0.1 mg PO once daily. Apixaban was also discontinued and replaced by clopidogrel because of the syncope and fall risk. All other medications remained the same. The patient's BP prior to discharge was 132/66 mmHg.

Table 1 Case 1: Patient's Selected Laboratory Values

Laboratory Parameter	Normal Range	Patient's Result on First Admission	Patient's Result on Second Admission
Serum sodium (Na)	135–145 mEq/L	140 mEq/L	134 mEq/L
Serum blood urea nitrogen (BUN)	8–21 mg/dL	48 mg/dL	44 mg/dL
Serum creatinine (SCr)	0.6–1.2 mg/dL	2.5 mg/dL	2.1 mg/dL
BUN:SCr ratio	10:1–20:1	19.2:1	21:1
Serum glucose	70–140 mg/dL	200 mg/dL	295 mg/dL
A1c	4.0–5.6%	8.0 %	
Random cortisol level	10–20 ng/dL	28.9 ng/dL	
Thyroid stimulating hormone (TSH)	0.36–5.8 uIU/mL	1.027 uIU/mL	
Free T_4	0.89–1.76 ng/dL	1.20 ng/dL	

One month later, the patient presented again following a syncopal episode. He reported adherence to all his medications. His major symptom upon admission was general malaise. His BP was measured at 79/65 mmHg. Pertinent laboratory data are listed in Table 1. All other laboratory parameters were within normal limits. Skin turgor, mucous membranes, and extremities also were within normal limits.

The patient's head and cervical spine CT scans were negative, and the ECG showed NSR. No ventricular arrhythmias were noted. Over the next five days, orthostatic testing was negative. His BP improved with metoprolol and torsemide on hold, and he was able to ambulate with no decline in BP.

At discharge, metoprolol, chlorthalidone, eplerenone, isosorbide mono-

Figure 1 Patient 1's Blood Pressure Trend (first admission only)

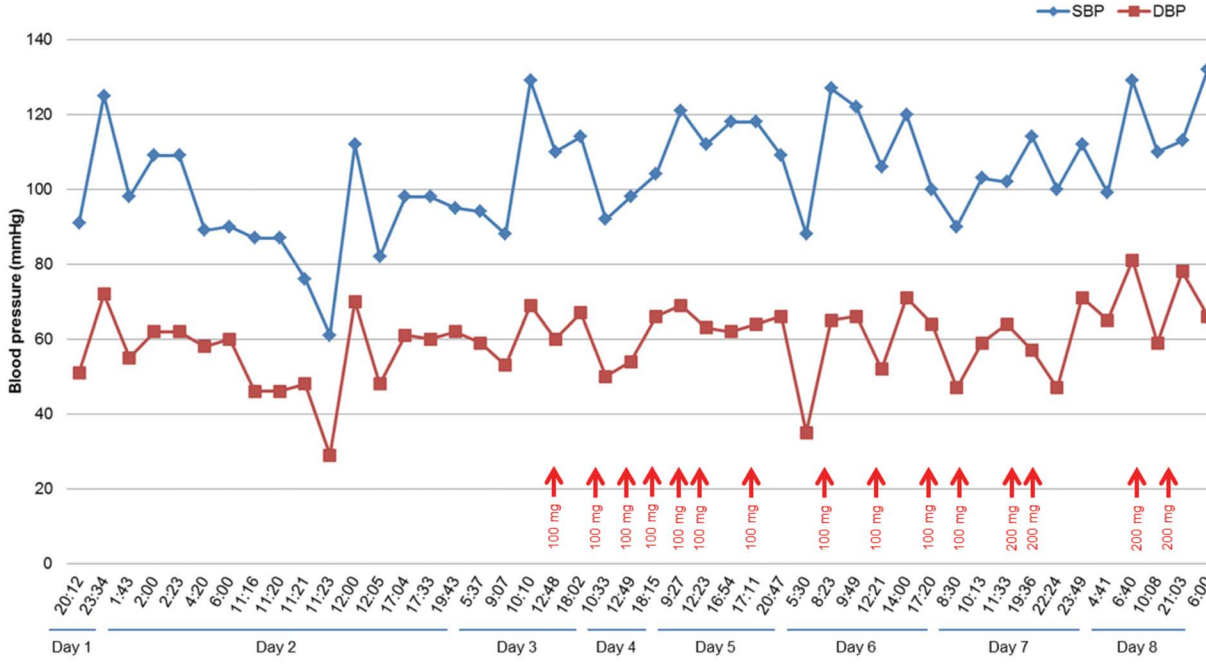


Table 2 Case 2: Patient's Selected Laboratory Values

Laboratory Parameter	Normal Range	Patient's Result
Serum sodium (Na)	135–145 mEq/L	155 mEq/L
Serum potassium (K)	3.6–5.2 mEq/L	3.6 mEq/L
Serum chloride (Cl)	98–107 mEq/L	106 mEq/L
Serum blood urea nitrogen (BUN)	8–21 mg/dL	43 mg/dL
Serum creatinine (SCr)	0.6–1.2 mg/dL	0.6 mg/dL
BUN:SCr ratio	10:1–20:1	72:1
Serum glucose	70–140 mg/dL	184 mg/dL
A1c	4.0–5.6%	5.9%
Arterial blood gas (pH)	7.35–7.45	7.06
Partial pressure of CO_2 (pCO_2)	35–48 mmHg	21 mmHg
Partial pressure of oxygen (pO_2)	83–108 mmHg	332 mmHg
Bicarbonate	19–23 mmol/L	5.9 mmol/L
Lactate	0.5–2.2 mmol/L	3.5 mmol/L
White blood cell count	3.9–11.0 K/uL	13.1 K/uL
Random cortisol level	10–20 ng/dL	17.1 ng/dL
Thyroid stimulating hormone (TSH)	0.36–5.8 uIU/mL	0.663 uIU/mL
Free T_4	0.89–1.76 ng/dL	1.09 ng/dL
Creatine phosphokinase	42–284 IU/L	> 9,400 IU/L
Troponin	0–0.5 ng/mL	30 ng/mL

nitrate, and metolazone were held. Atorvastatin was held because of a history of myalgias, and torsemide was changed to bumetanide. Droxidopa 200 mg TID and fludrocortisone 0.1 mg once daily-were continued. His BP prior to discharge was 117/70 mmHg. Upon exclusion of hypovolemia and other neurodegenerative diseases, the etiology of the patient's orthostatic dysfunction was thought to be a result of autonomic dysfunction from long-standing T2DM, despite the use of medications known to cause hypotension such as diuretics and beta blockers.

CASE 2

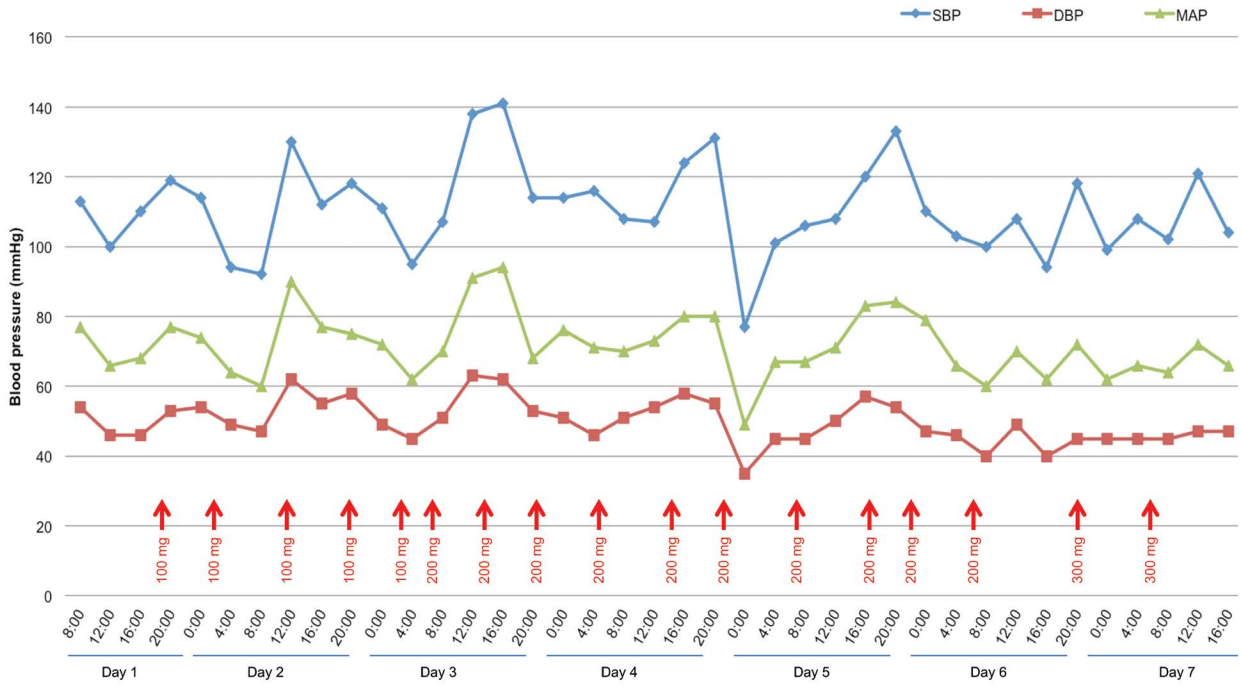
A 75-year-old Caucasian female was brought to the ED after her family found her on the floor, where she had lain for over 24 hours. Her medical history was significant for severe intractable RA with severe deformities of the upper extremities, T2DM, severe malnutrition with a 30–40 pound weight loss over the previous two years, and depression. She had a reported allergy to penicillin (hives). For the last four years, she had refused medications, with the exception of ibuprofen, and had a poor appetite. Her vital signs upon arrival were: temperature 37.6°C, BP 70/50 mmHg, HR 106 bpm, RR 26 breaths per minute, and SpO_2 of 100% (on non-rebreather mask). She had pre-renal azotemia and severe dehydration based on her BUN/SCr ratio of 72:1 and was found to have severe metabolic acidosis per her arterial blood gas results (see Table 2 for patient's laboratory values obtained on admission). She was suspected of having systemic inflammatory response syndrome based on her clinical and laboratory presentation. She was treated with norepinephrine (NE) at a rate of up to 30 µg/min, two units of packed red blood cells, five ampules of sodium bicarbonate 50 mEq, meropenem 1 g every 12 hours, vancomycin 750 mg intravenously (IV) every 12 hours, and received fluid resuscitation. As she was in respiratory failure, she underwent intubation, and a CT pan scan was performed. Scan results revealed a T8 compression fracture, whereupon she was transferred to the surgical intensive care unit (SICU).

In the SICU, the patient was noted to have rhabdomyolysis and an active non–ST-elevation myocardial infarction (NSTEMI). Her creatine phosphokinase level was greater than 9,400 IU/L (normal value [NV], 42–284 IU/L) and her maximum troponin level was 30 ng/mL (NV, 0–0.5 ng/mL). She had no distal pulses in the right lower extremity due to right femoral artery dissection. This was a result of an emergency femoral line placement. A CT angiography revealed the presence of a thrombus from the external iliac to the superficial femoral artery with dissection, in which she received heparin 550 units/hr IV. She lost perfusion to her right leg and subsequently underwent an above-knee amputation. She continued to be on high doses of NE up to 30 mcg/min and vasopressin 2.4 units/hr to maintain her BP, but these were held for the latter half of day 3. On day 4, she developed acute kidney failure and fluid overload. Her SCr was 1.5 mg/dL (baseline, 0.6 mg/dL), fluid input was 5 L/24 hr, and urine output was 1 L/24 hr (net, +4 L). The etiology was likely multifactorial because of rhabdomyolysis, hemodynamic instability, and contrast-induced nephropathy after receiving multiple imaging scans requiring IV contrast (Omnipaque™ 300). As a result, the patient was initiated on furosemide 40 mg IV daily, aggressive hydration (lactated ringers 75 mL/hr), and continuous renal replacement therapy. While on furosemide, she became hypotensive with two subsequent BP readings of 99/45 mmHg and 97/42 mmHg. NE administration was restarted at an average rate of 7 mcg/min with a range of 2 mcg/min to 12 mcg/min.

Throughout her hospitalization, the patient was hypotensive and required intermittent NE support for the majority of her admission. She initially presented with dehydration based on her BUN/SCr ratio, which was subsequently corrected with fluids. On day 27, her morning random cortisol level was 17.1 µg/dL (NV, 10–20 ng/dL). At this point, dehydration and adrenal insufficiency were ruled out as the etiologies of her hypotension. Also, she was not suspected to have hypothyroidism based on her thyroid panel results of thyroid stimulating hormone (TSH) 0.663 uIU/mL and free T_4 1.09 ng/dL.

After day 24, she was initiated on midodrine 5 mg TID for pressor support, with intermittent doses of NE at an average rate of 3 mcg/min (range, 1–7 mcg/min). Her mean arterial pressure (MAP) was above the target of > 65 mmHg after one day of midodrine. NE was subsequently discontinued. Despite this initial improvement, NE was restarted at an average of 2 mcg/min (range, 1–3 mcg/min) and midodrine was eventually

Figure 2 Patient 2's Trend of Blood Pressure Measurements and Droxidopa Administration



titrated up to the maximum recommended dose of 15 mg TID as a result of her decreasing BP response. As this dosage of midodrine administered for 11 days failed to consistently maintain her MAP > 65 mmHg, she was switched over to droxidopa 100 mg TID.

After the first two doses of droxidopa 100 mg were administered, the patient became transiently hypotensive (BP, 94/49 mmHg and 92/47 mmHg) and slightly tachycardic (HR, 115 bpm) (see Figure 3). She was maintained on the same strength of this medication for three additional doses. Her subsequent BP and HR were recorded as 95/45 mmHg and 62 bpm, respectively. Droxidopa was then titrated up to 200 mg TID. She received this for 10 doses before it was further titrated up to 300 mg TID (see Figure 2 for patient's BP response). Droxidopa was finally discontinued after she received two of these doses as a result of her continuous need for NE support and tachycardia (HR, 126 bpm four hours after receiving her last dose). While on droxidopa, her HR was greater than 100 bpm 62% of the time and greater than 110 bpm 28% of the time (see Table 3 for her HR and BP measurements). She was restarted on midodrine 15 mg PO TID and eventually weaned off NE 11 days thereafter. Her subsequent HR values remained mostly within normal limits. When stable (at day 61 of admission), she was discharged to a rehabilitation facility, receiving midodrine 15 mg PO TID. Her final BP, MAP, and HR readings prior to discharge were as follows: 120/55 mmHg, 62 mmHg, and 101 bpm, respectively.

DISCUSSION

Previous studies on droxidopa for the treatment of nOH show varying results. In a dose response, safety, and tolerability study, Mathias et al. evaluated 32 patients (n = 26 with multiple system atrophy and n = 6 with pure autonomic failure) over 10 weeks and showed that droxidopa significantly increased SBP during an orthostatic challenge.[5] Orthostatic hypotension resolved in 14 (44%) patients. Symptom scores, such as lightheadedness, dizziness, and blurred vision, also improved: –2.00 (baseline value, 5.00; $P = 0.0625$), –1.11 (baseline value, 4.65; $P = 0.0931$), and –3.67 (baseline value, 5.83; $P = 0.0313$), respectively. Two serious adverse events, laryngeal dyspnea and syncope, were reported as possible complications of underlying diseases.

A randomized, placebo-controlled, phase 3 trial by Kaufmann et al. evaluated the effects of droxidopa in 162 patients with nOH from PD, multiple system atrophy, pure autonomic failure, or non-diabetic autonomic neuropathy.[6] Droxidopa significantly improved the Orthostatic Hypotension Questionnaire (OHQ) composite score (see Figure 4) (mean change, 0.90 units; $P = 0.003$), with the greatest change noted in dizziness and lightheadedness. Mean standing and supine SBP also significantly increased in the droxidopa group compared to the placebo group (11.2 vs. 3.9 mmHg, $P < 0.001$; 7.6 vs. 0.8 mmHg, $P < 0.001$, respectively). The double-blind treatment period was only one week in duration, a notable limitation of this study.

Isaacson et al. sought to determine droxidopa effects in the long-term management of nOH in 102 patients in a 12-month study.[7] Improvements in the OHQ composite score exceeded 50% after one month of droxidopa therapy; this effect persisted until the study's end. A potential limitation was that the study was only double-blinded for the first two weeks of treatment, during which the difference between droxidopa and placebo was statistically insignificant. In a different study with 51 patients with PD, droxidopa-treated patients did not meet the primary efficacy endpoint of mean change in OHQ composite score

Table 3 Case 2: Patient's SBP, DBP, MAP, and HR Readings While Receiving Droxidopa

Day of Droxidopa Therapy	Time	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)	HR (bpm)
1	20:00	119	53	77	98
	00:00	114	54	74	102
	4:00	94	49	64	115
	8:00	92	47	60	106
2	12:00	130	62	90	129
	16:00	112	55	77	96
	20:00	118	58	75	102
	00:00	111	49	72	96
	4:00	95	45	62	62
	8:00	107	51	70	86
3	12:00	138	63	91	111
	16:00	141	62	94	115
	20:00	114	53	68	109
	00:00	114	51	76	104
	4:00	116	46	71	100
	8:00	108	51	70	95
4	12:00	107	54	73	97
	16:00	124	58	80	103
	20:00	131	55	80	104
	00:00	77	35	49	89
	4:00	101	45	67	86
	8:00	106	45	67	84
5	12:00	108	50	71	103
	16:00	120	57	83	132
	20:00	133	54	84	116
	00:00	110	47	79	106
	4:00	103	46	66	99
	8:00	100	40	60	81
6	12:00	108	49	70	107
	16:00	94	40	62	103
	20:00	118	45	72	115
	00:00	99	45	62	109
	4:00	108	45	66	110
	8:00	102	45	64	109
7	12:00	121	47	72	126
	16:00	104	47	66	118

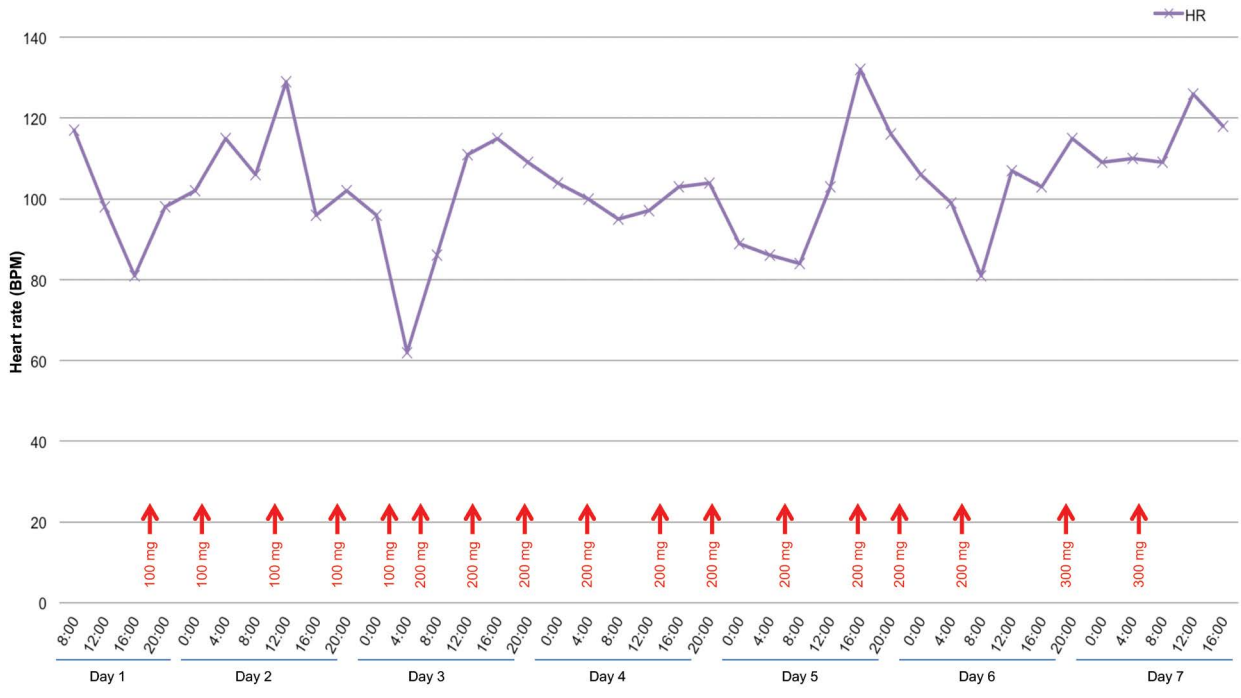
from baseline to end of study compared to placebo-treated patients (–2.2 vs. –2.1; $P = 0.98$). Nevertheless, there were some nonsignificant benefits associated with droxidopa. The mean dizziness/lightheadedness score change favored droxidopa by 1.5 units ($P = 0.24$), and the mean standing SBP change favored droxidopa by 12.5 mmHg ($P = 0.04$). Also, droxidopa-treated patients had a 50% lower rate of reported falls ($P = 0.16$).[8]

The general approach to treating orthostatic hypotension starts with nonpharmacological measures. These include discontinuing medications which may be causative, diet modification, limiting the use of alcohol, increasing water and sodium consumption, specific physical maneuvers, and wearing compression stockings. Medications that can increase BP can be trialed in patients who fail nonpharmacological therapy. Fludrocortisone is a synthetic mineralocorticoid considered to be the first-line agent for treating orthostatic hypotension. Sympathomimetic medications, such as the peripheral alpha$_1$-adrenergic agonist midodrine, can be added if patients are still inadequately managed.[9]

In the first case, the patient's medical history was significant for peripheral neuropathy with the absence of other causes. Neurodegenerative disease and hypovolemia contributed to his diagnosis of persistent orthostatic hypotension as a result of diabetic neuropathy-associated autonomic dysfunction. Many of the antihypertensive and cardiac medications he was taking could have also played a causative role. It is difficult to assess which specific medications could have had the greatest effect on the patient's BP because he was not monitored for de-escalation for each one, and many of them were needed to manage his comorbid conditions.

Droxidopa 100 mg PO TID and fludrocortisone 0.1 mg PO once daily were initiated when midodrine monotherapy was found to be insufficient for managing the orthostatic hypotension. Although he did not test positive for orthostatic hypotension on the second admission while receiving droxidopa, the patient was still admitted for multiple daily syncopal episodes. His BP increased when metoprolol and torsemide were held and droxidopa 200 mg TID was used. His response to droxidopa was difficult to assess as he was initiated on it at the same time as the fludrocortisone. Droxidopa may have been useful in stabilizing his BP (i.e., no decline in SBP > 20 mmHg or DBP > 10 mmHg) when he changed positions. However, droxidopa did not help prevent syncopal episodes in this patient. It is also pertinent to note that the maximum dose used was 600 mg per day, whereas the maximum daily

Figure 3 Patient 2's Trend of Heart Rate Measurements and Droxidopa Administration



dose of droxidopa is 1,800 mg. Further up-titration of the medication may have produced a better outcome for him, but it was not tried.

In the second case, the patient's medical history was negative for a nerve disorder and she was not found to be hypovolemic as she experienced frequent episodes of being fluid-overloaded. Her home medications were unlikely to have contributed to her hypotension as she had stopped taking medications, except ibuprofen, over the previous four years. The only anti-hypertensive medications she received in the hospital were loop and thiazide diuretics as needed for fluid overload. Hypothyroidism and adrenal insufficiency were unlikely to be the cause of her hypotension due to normal thyroid and cortisol levels. However, she did have intractable RA with severe upper extremity deformities, and had not received treatment for many years. Edmonds et al. demonstrated that RA was associated with an increased incidence of autonomic neuropathy, particularly an abnormal cardiovascular reflex.[10] Furthermore, Saba et al. conducted a study of 25 subjects with RA and 30 healthy control subjects that showed a significant decrease in standing SBP and DBP measurements in patients with RA compared to those in healthy subjects.[11] Similarly, Geenan et al. studied the autonomic responses of 21 patients with RA compared to 20 healthy control subjects and found that the patients with RA had diminished autonomic responses compared to the healthy subjects, particularly with regard to the SBP response.[12] A literature review completed by Stojanovich revealed that many patients with RA have evidence of autonomic dysfunction, including orthostatic hypotension.[13] As other causes were ruled out in case 2, autonomic dysfunction associated with RA remained the likely etiology of the patient's hypotension.

The patient received midodrine 5 mg TID to treat her persistently low BP and to wean her off vasopressor support. Although her BP increased initially, it subsequently decreased, therefore the midodrine was titrated up to the maximum recommended dose of 15 mg TID. This was given with intermittent doses of NE. The midodrine was then discontinued, and the droxidopa was re-started and continued for a total of 17 doses, but it did not produce successful results. Although 77% of her MAP readings were above her target of > 65 mmHg, she remained hypotensive and needed intermittent NE administration. She was also tachycardic, with 62% of her HR readings above 100 bpm.

Although the droxidopa trial was unsuccessful in this patient, she may have benefited from a decreased dose of midodrine (starting at the lowest dose of 2.5 mg TID) with concurrent droxidopa administration (starting at 100 mg TID). These two medications have different mechanisms of action and can have an additive effect. Midodrine converts into the active metabolite desglymidodrine (an $alpha_1$-adrenergic agonist[14]) whereas droxidopa is metabolized to NE, exerting its effects on $beta_1$-adrenergic and alpha-adrenergic receptors. Currently, tachycardia is not a reported adverse effect of droxidopa, but droxidopa's effect on the $beta_1$-adrenergic receptors could explain why the patient's HR was elevated when the dosage was increased. When combining therapy, the addition of more agonistic effects on the $alpha_1$-adrenergic receptors from midodrine may have increased her BP and allowed for lower doses of droxidopa, which would decrease the effect on HR. Further, fludrocortisone (a synthetic mineralocorticoid that expands plasma volume and increases vascular alpha-adrenergic receptor sensitivity)[15] could also have been tried in combination with

continued on page 143

continued from page 130

Figure 4 Orthostatic Hypotension Questionnaire (OHQ)6

ORTHOSTATIC HYPOTENSION SYMPTOM ASSESSMENT (OHSA)

Please tick the number on the scale that best rates how severe your symptoms from low blood pressure have been on average over the past week. You should respond to every symptom. If you do not experience a symptom, circle zero (0). YOU SHOULD RATE ONLY THE SYMPTOMS THAT ARE A RESULT OF YOUR LOW BLOOD PRESSURE PROBLEM.

1. Dizziness, lightheadedness, feeling faint, or feeling like you might black out												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*
2. Problems with vision (blurring, seeing spots, tunnel vision, etc.)												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*
3. Weakness												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*
4. Fatigue												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*
5. Trouble concentrating												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*
6. Head/neck discomfort												
None	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Worst Possible*

ORTHOSTATIC HYPOTENSION ACTIVITY SCALE (OHDAS)

We are interested in how the low blood pressure symptoms that you experience affect daily life. Please rate each item by ticking the number that best represents how much on average the activity has been interfered with over the past week by the low blood pressure symptoms you have experienced. If you cannot do the activity for reasons other than low blood pressure, please check the box at right.

													Cannot do for other reasons
1. Activities that require standing for a short time													
No interference	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Complete interference*	☐
2. Activities that require standing for a long time													
No interference	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Complete interference*	☐
3. Activities that require walking for a short time													
No interference	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Complete interference*	☐
4. Activities that require walking for a long time													
No interference	0 ☐	1 ☐	2 ☐	3 ☐	4 ☐	5 ☐	6 ☐	7 ☐	8 ☐	9 ☐	10 ☐	*Complete interference*	☐

droxidopa and/or midodrine. Combining the drugs' different mechanisms of action could raise BP with a minimal effect on HR. However, as this patient had undergone an above-knee amputation, there was concern about wound-healing impairment with fludrocortisone use, and it was not administered.[16]

CONCLUSION

Droxidopa is approved for the treatment of nOH caused by primary autonomic failure. Sometimes, droxidopa is trialed in other uses as a last-line agent; however, the cases presented here add to the existing literature demonstrating that droxidopa may have varying effects in treating orthostatic hypotension caused by diabetes-related autonomic dysfunction and non-neurogenic etiologies, such as RA.

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