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Droxidopa for refractory neurogenic orthostatic hypotension in amyloid light chain amyloidosis

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ABSTRACT

Neurogenic orthostatic hypotension (nOH) secondary to amyloidosis is a rare condition associated with significant blood pressure (BP) drops and problematic symptoms for patients. There is limited literature on the management of nOH secondary to amyloidosis. In this report, we describe a case on a 60-year-old female with an extensive past medical history, including amyloidosis, pulmonary hypertension, heart failure with preserved ejection fraction, and episodic hypotension, who presents to the hospital with dizziness and home systolic BP readings in the 80s. Due to hypoperfusion, she eventually developed acute kidney failure and was transferred to the intensive care unit (ICU) for intermittent continuous renal replacement therapy with pressor support using norepinephrine. She had difficulty maintaining adequate BPs while on midodrine, so fludrocortisone, followed by pseudoephedrine, were added to improve her pressures. She was subsequently transferred out of the ICU, but her BPs still remained low, and she was not able to sit up without getting dizzy. Droxidopa was eventually added on to help treat her refractory nOH. After droxidopa initiation, her BPs improved and she was able to sit up without dizziness and was finally discharged home. This case report demonstrates the therapeutic usefulness of droxidopa in improving both BPs and symptoms in refractory nOH secondary to amyloidosis.

Keywords: Droxidopa, Neurogenic orthostatic hypotension, Amyloidosis

INTRODUCTION

Amyloidosis is a rare disease and refers to a collection of 30 protein-folding diseases where patients develop extracellular deposition of different insoluble protein fibrils into various tissues and organs. Extracellular deposition of protein fibrils can lead to inflammation and complications of organ dysfunction and failure.[1] Depending on the type of amyloidosis, different organs can be affected and can include the skin, heart, nerves, kidneys, and the liver. Neurologic involvement can include both autonomic and peripheral neuropathy. Patients with autonomic neuropathy can develop various manifestations including blurry vision, heat intolerance, urinary hesitancy, and orthostatic hypotension. Neurogenic orthostatic hypotension (nOH) in amyloidosis patients can develop secondary to amyloid fibril deposits in neurons.[2]

nOH is a subtype of orthostatic hypotension and is caused by the insufficient release of norepinephrine in post-ganglionic sympathetic neurons due to autonomic dysfunction.[3] Major causes of nOH generally include Parkinson's Disease, Multiple System Atrophy, Pure Autonomic

Failure, and Dementia with Lewy Bodies. nOH secondary to amyloidosis can be problematic for patients and difficult to manage. Several non-pharmacologic measures can be used in patients with nOH and syncope and include acute water ingestion for temporary relief, physical counter-pressure maneuvers (leg crossing, maximal force handgrip, etc.), and compression garments. Pharmacotherapy is generally reserved for patients with severe symptoms or whose symptoms are not controlled by non-pharmacologic therapy alone.[1] The 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope makes a moderate recommendation (IIa) for midodrine, droxidopa, and fludrocortisone suggesting these agents can be effective and beneficial for nOH.[4] Both midodrine and droxidopa have moderate quality of evidence (Level B-R), while fludrocortisone has more limited data (Level C-LD).

While midodrine and fludrocortisone can be used for treating nOH, droxidopa is a new therapeutic agent that is specifically Food and Drug Administration (FDA)-approved for this indication. Droxidopa has been primarily studied in Parkinson's associated nOH where it has demonstrated short-term improvement in symptoms and blood pressure (BP).[5] There are limited studies of droxidopa use in amyloidosis patients. One small retrospective observational study evaluated droxidopa use in severely ill hospitalized patients and found that amyloidosis patients did have BP improvements.[6] In this case report, we present an acutely ill patient with severe amyloidosis of the heart, lungs, and kidneys and severe refractory nOH. We describe the stepwise addition of fludrocortisone**,** then pseudoephedrine and finally droxidopa for the successful treatment of refractory nOH.

CASE REPORT

A 60-year-old female arrived at the emergency department (ED) complaining of shortness of breath (SOB), chest pressure, dizziness, and weakness. She reported home systolic BP (SBP) readings in the 80s despite taking midodrine 10 mg three times daily (TID). She has a past medical history of AL amyloidosis, Type 1 pulmonary arterial hypertension, diabetes, coronary artery disease, chronic kidney disease stage IIIb, heart failure with preserved ejection fraction (EF), obstructive sleep apnea, severe esophagitis, diffuse anasarca, and episodic hypotension. Family history was significant for mother, sister, and aunts who have breast cancer. Social history was negative for alcohol, smoking, or illicit drugs.

On presentation, her vitals were BP 105/64 (mmHg), heart rate (HR) 89 beats per minute (BPM), respiratory rate 18 breaths per minute, with a temperature of 98.4°F. Her oxygen saturation was 92% on room air, and she was placed on oxygen via nasal cannula. Her laboratories were significant for a blood urea nitrogen of 30 mg/dL, serum creatinine (SCr) of 3.9 mg/dL (baseline SCr 2.5 mg/dL), troponin of 0.48 ng/mL, brain natriuretic peptide (BNP) of 3175 pg/mL, and a total protein of 4.7 g/dL and an albumin of 2.2 g/dL. Her SBP remained in the 100 s, HR 80–90 BPM, and pulse oximetry was 95% on 4L of oxygen via nasal cannula. Her body max index was 31.7 kg/m^2 with a body weight of 83.7 kg. In the ED, she received lactated ringers 250 mL and ceftriaxone 2 g intravenously. Chest X-ray showed bilateral lower lobe airspace opacities and moderate right pleural effusion.

For her acute respiratory failure and SOB, pneumonia was not likely as she was afebrile, had a normal white blood cell count and low procalcitonin. Hence, antibiotics were not continued by the primary medical team. Her SOB was multifactorial due to her congestive heart failure (CHF) and pulmonary hypertension, both complications from her amyloidosis. Further work-up of her pleural effusion through chest ultrasound showed 200 mL of pleural effusion in both lobes of the lung. Due to the smaller volume, a thoracentesis was not pursued. Her mildly elevated troponin was not significant as it was in the range of her prior troponin (0.42 ng/mL). She continued to receive oral riociguat and selexipag for her pulmonary hypertension. Her elevated BNP and anasarca were attributed to CHF and acute kidney injury in the setting of chronic kidney disease. A recent echo demonstrated EF 50–55% and grade 3 diastolic dysfunction. Nephrology recommended low dose IV furosemide at 20 mg TID and she often missed doses due to low BPs. To improve her volume status and tolerability to furosemide, albumin 12.5 g IV was given as needed. The patient was diagnosed 2 months ago with AL amyloidosis by kidney biopsy. According to oncology, she had a poor prognosis for amyloidosis due to heart, lung, and kidney involvement. She had started chemotherapy (daratumumab, cyclophosphamide, bortezomib, and dexamethasone) for amyloidosis 1 month prior, and oncology continued her treatment during this hospital course with goals to improve heart, lung, and kidney function. She was given a poor prognosis of 4–6 months, but she elected to continue chemotherapy.

Her SBPs remained consistently at 80 mmHg while on midodrine 10 mg TID. She continued to complain of dizziness on standing so physical therapy was ordered. A morning plasma cortisol level was within normal limits at 8 μg/dL, hence adrenal insufficiency was ruled out. Although her pulmonary hypertension medications, particularly riociguat, could have been contributing to her dizziness and hypotension, it was continued in efforts to maintain effective treatment for her pulmonary disease. Cardiology was consulted on day 9 of hospital stay and recommended adding fludrocortisone 0.2 mg daily, liberal salt intake, and holding furosemide. Albumin was also continued as her low BP were also likely due to her hypoalbuminemia. Inotropes were not recommended based on her normal EF. Her BP

increased slightly to 86/54 mmHg (mean) with a range of 74/42 mmHg to 97/61 mmHg, but still remained low. Over the next few days, her kidney functioned worsened due to hypoperfusion (SCr 5.9 mg/dL) and her anasarca increased. Nephrology transferred her to the intensive care unit for continuous renal replacement therapy (CRRT) with pressor support using norepinephrine. Intermittent small volume CRRT was successfully completed with norepinephrine support for several days. Her BP was 99/67 mmHg (mean) with a range of 91/63–117/68 mmHg and her mean arterial pressures were >60 mmHg, but she was still requiring higher doses of norepinephrine. To wean her off the norepinephrine, several therapeutic strategies were completed and included: Midodrine dose increase to 17.5 mg TID, followed by fludrocortisone dose increase to 0.3 mg daily, and finally the addition of pseudoephedrine 60 mg Q6H 2 days later. With adjustments in the medications, her BPs increased to the 100/80s and she was slowly weaned off the norepinephrine. However, she continued to have symptomatic orthostatic hypotension upon standing. On day 24 of hospitalization, cardiology recommended droxidopa 100 mg TID for additional BP support and to help wean off the fludrocortisone. Fludrocortisone dose was decreased to 0.2 mg daily as cardiology was concerned about sodium and fluid retention with higher doses of fludrocortisone. Droxidopa doses were titrated up to 300 mg TID over the next few days and her BP increased to 109/78 mmHg (mean) with a range of 80/45–121/73 mmHg. Her SBP steadily improved to 100–115 mmHg with droxidopa initiation, although she still had some episodic drops to 80–90 mmHg due to intermittent hemodialysis. On day 36, the patient was able to sit on edge of bed without getting dizzy. On day 38, the patient was able to be transferred to a wheelchair and finally discharged a few weeks later.

DISCUSSION

Droxidopa (Northera®) capsules was approved on February 18, 2014, by the FDA for the treatment of orthostatic hypotension.[7] Droxidopa is the l-isoform of 3,4-threo-dihydroxyphenylserine and has a similar structure to levodopa with the addition of a hydroxyl group. Droxidopa is a prodrug that is converted to norepinephrine by the enzyme aromatic amino acid decarboxylase. This enzyme is ubiquitously expressed throughout the body.[8]

Most studies on the efficacy of droxidopa for nOH are small and primarily involve patients with Parkinson's disease.[9-11] Literature evidence of droxidopa for refractory nOH in AL amyloidosis patients is very limited and is comprised one retrospective study and one case report.[6,12] The retrospective study involved 20 hospitalized, severely ill patients with refractory nOH. Patients were refractory to midodrine and/or fludrocortisone and had nOH secondary to various causes including amyloidosis, multiple system atrophy, autoimmune autonomic neuropathy, pure autonomic failure, diabetes, end-stage renal disease, and Parkinson's disease. The mean baseline standing SBP before droxidopa was 97 ± 26 mm Hg. Droxidopa doses were titrated over 1–6 days and the final average daily droxidopa dose was 837 ± 509 mg. Following dose titration, the final mean standing SBP was 98 ± 17.5 mmHg. Although there was a lack of significant BP improvements in all patients, the study found that the amyloidosis group had the most significant decrease in SBP drops between supine and standing on treatment (28 mm Hg at baseline vs. 11.2 mm Hg post-treatment). Amyloidosis patients also required higher doses compared to other groups (mean daily dose 1000 mg vs. 793 mg).[6] The one published case report we identified described a 64-year-old man who presented with syncope and was eventually diagnosed with AL amyloidosis and myeloma.[12] He continued to have repeated episodes of hypotension and bradycardia while taking midodrine and fludrocortisone. Droxidopa 200 mg TID was started and his BPs improved and the dose was increased to 300 mg TID. The patient's BP, HR, and ability to sit upright significantly improved after droxidopa initiation.[12]

Our presented case is distinctive because we describe a patient with nOH secondary to severe AL amyloidosis who was given multiple therapeutic agents for refractory nOH including midodrine, fludrocortisone, pseudoephedrine, and droxidopa. The published case report mentioned earlier described the use of midodrine, fludrocortisone, and droxidopa for nOH in AL amyloidosis.[12] For our case, pseudoephedrine helped to wean the patient off the norepinephrine drip and thus is a potential option for treating nOH. Our patient's BPs remained low while on midodrine, fludrocortisone, and pseudoephedrine. The patient did require intermittent CRRT due to her failing kidney function. This could have been a factor in her continued low BPs, but many CRRT sessions had to be canceled considering her low BPs. Subsequent droxidopa initiation increased the patient's SBPs to 100–115 mmHg from the 90 to 100 s mmHg. The patient was also able to tolerate CRRT and sit up without being hypotensive several days after droxidopa started. It is possible that her amyloidosis responded to her chemotherapy which may have helped her improve clinically. However, the timeline in which BP and symptomatic improvements were seen after droxidopa initiation were relatively fast in terms of onset and hence we felt it can be attributed to droxidopa. A meta-analysis published in 2017, demonstrated that droxidopa increased SBPs by 11.5 ± 20.5 mmHg in patients with nOH.[11] Our patient's SBPs increased by an average of 10 mmHg. Available studies with droxidopa assessed efficacy based on symptomatic improvement using the Orthostatic Hypotension Questionnaire which includes the 6-item Orthostatic Hypotension Symptom Assessment scale. All

studies showed symptomatic improvement, particularly in dizziness and lightheadedness.[9-11] Our patient had marked improvement in symptoms and function following droxidopa. A drawback to droxidopa's effects is that its benefits appear to be short-lived lasting only 1–2 weeks. Its effectiveness beyond 2 weeks needs to be more extensively assessed in all patients. For this patient case, the patient remained in the hospital for 2 weeks following initiation of droxidopa and after 1 week of therapy, her BPs remained in 110 s/80 s mmHg. Her BP did start to drop to the low 100 s 2 weeks after initiation. However, she was able to continue to sit upright without dizziness and this allowed for hospital discharge with home health and physical therapy.

CONCLUSION

Overall, droxidopa was effective in treating our patient with refractory nOH. It allowed for clinical improvement in our patient's BPs, symptoms, and function. It also allowed for fludrocortisone dose-sparing. Although clinical effects may be short-lived, droxidopa can be an effective option in treating refractory nOH. More studies are needed to assess its long-term efficacy.

Declaration of patient consent

Patient's consent not required as patient's identity is not disclosed or compromised.

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Conflicts of interest

There are no conflicts of interest.

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