Published in final edited form as:

Auton Neurosci. 2016 July ; 198: 8–9. doi:10.1016/j.autneu.2016.07.002.

Neurogenic Orthostatic Hypotension with Critical Illness Neuropathy treated with Droxidopa

Baxter B. Allen, MD¹, James A. Charles, MD², Esperanza Papadopoulos, MD³, and Edward K. Avila, DO⁴

¹Department of Neurology, Weill Cornell Medical College, New York, NY

²Department of Neurology, Rutgers Medical School, Newark, New Jersey

³Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

⁴Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY

Keywords

Neurogenic; orthostatic; hypotension; neuropathy; droxidopa

Orthostatic hypotension (OH) may occur due to neurogenic or non-neurogenic causes. Neurogenic orthostatic hypotension (NOH) can occur secondary to central and peripheral processes. Peripheral neuropathies due to diabetes, autoimmune disease, vitamin deficiencies, and critical illness may cause NOH. Central causes include Parkinson's disease, disorders of multisystem degeneration, and brain trauma. Non-neurogenic causes include cardiac impairment, reduced intravascular volume, and vasodilation. Common drugs that cause OH are diuretics, alpha-adrenoceptor blockers, antihypertensives, and calcium channel blockers. Hydrochlorothiazide, lisinopril, trazodone, furosemide, terazosin and tricyclic antidepressants can also cause vasodilation and OH in predisposed patients. (1)

We report the first case of a patient with NOH secondary to critical illness neuropathy, whose OH resolved with the use of droxidopa when all other agents failed. The patient is a 66-year-old man with a history of acute myelogenous leukemia status post stem cell transplant 2 years prior to presentation, and diabetes, who developed ehrlichiosis from a tick

Corresponding Author: Edward K. Avila, D.O., Department of Neurology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065, Phone #: (212) 639-3718, Fax #: (646) 422-2174, avila@mskcc.org.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Dr. Allen contributed to the drafting and editing

Dr. Charles contributed to the drafting and editing

Dr. Papadopoulos contributed to the drafting and editing

Dr. Avila contributed to the drafting, editing, and all final decisions

Dr. Allen has no conflict of interest

Dr. Charles has no conflict of interest

Dr. Papadopoulos has no conflict of interest

Dr. Avila has no conflict of interest

bite and went into septic shock. He had a normal neurologic examination during a routine clinic visit 2 days prior to his acute illness without complaints of numbness or tingling. He was in the ICU for 29 days, where he required mechanical ventilation, vasopressors and antibiotic therapy. He was vent-dependent for 16 days, and tracheostomy was reversed after 35 days. Examination revealed marked length-dependent weakness, minimal sensory loss, and areflexia in the lower extremities. Electromyography and nerve conduction velocity studies revealed axonal changes without demyelination or conduction block, consistent with an axonal sensorimotor neuropathy, leading to the diagnosis of critical illness neuropathy.

With intensive physical therapy, he recovered enough strength to stand, but was unable to remain upright due to significant orthostasis, 145/89 mmHg supine to 96/75 mmHg standing, with a concomitant increase in heart rate from 83 to 115 beats per minute (BPM). Given the intact heart rate response, the patient also received multiple boluses of isotonic fluid without response, and had several echocardiograms which revealed no cardiac abnormalities or evidence of intravascular fluid depletion. Lab tests showed normalization of renal function from his earlier septic shock, with normal BUN to creatinine ratios. Vitamin B12 was supranormal, rapid plasma reagin was nonreactive; while serum glucose measurements varied significantly over the hospitalization with periodic measurements above 300 mg/dL, his hemoglobin A1C was 6.2% when rechecked due to the orthostatic hypotension after being measured at 8.0% at admission 6 weeks prior. He also complained of a few episodes of urinary retention and a loss of morning erections, which he had almost daily prior to the hospitalization.

Over 4 weeks, several pharmacologic therapies were initiated: pyridostigmine, which was slowly increased from 60 mg to 180 mg extended release daily; fludrocortisone, which was slowly increased from 0.1 mg to 0.5 mg daily; and midodrine, which was increased from 5 mg to 15 mg three times a day. Despite these therapies, he continued to have significant orthostasis, with blood pressures dropping from 157/70 mmHg supine to 90/60 mmHg sitting, with a concomitant increase in heart rate from 90 to 112 BPM.

Droxidopa was added and carefully titrated over two weeks to a dose of 500 mg three times a day. To avoid significant supine hypertension (i.e. SBP > 180 mmHg, DBP > 110 mmHg) from multiple antihypertensives, midodrine was slowly down-titrated to 2.5 mg three times a day, and the patient's blood pressure and heart rate were monitored every 4 hours while supine. At these doses, he maintained adequate standing blood pressure, despite ongoing orthostatic changes, with a decrease in blood pressure from 150/70 mmHg supine to 90/60 mmHg standing. He started to tolerate short walks, and over the course of the following week, his blood pressure further improved to 160/90 mmHg supine to 117/73 mmHg standing, with heart rate rising only from 85 to 90 BPM. He was discharged to subacute rehabilitation.

Four months later, fludrocortisone, pyridostigmine and midodrine were discontinued. He is currently on Droxidopa 300 mg three times a day, and has no further symptoms of orthostasis with orthostatic blood pressure measurements at his last clinic visit stable at 121/78 supine and standing.

Critical illness neuropathy (CIN) is a common complication of sepsis and multi-organ failure in patients admitted to the ICU, occurring in 25–63% of patients on a ventilator for at least 1 week, and 70–100% in patients with sepsis and multi-organ failure.^{2,3} CIN is suspected based on clinical features of prominent muscle weakness, absent or severely reduced deep tendon reflexes, and frequently significant sensory loss along with autonomic dysfunction. (4, 5) While there is no uniform diagnostic criteria for CIN, diagnosis is generally based on electrophysiologic testing: reduction in amplitudes and increased duration of compound muscle action potentials, decreased sensory nerve action potential amplitudes, fibrillation potentials and sharp waves on needle electromyography and eventually spontaneous activity, with generally normal conduction velocities, distal motor latencies and responses to repetitive nerve stimulation. Microcirculatory damage impairs peripheral nerve and muscle perfusion, and with reduced oxygen supply, these cells are under metabolic stress and are unable to generate action potentials. (2) In this specific case, given the intact heart rate response in the patient, concomitant non-neurogenic causes of orthostatic hypotension, including deconditioning, hypovolemia, and systemic malaise may have accounted for part of the drop in blood pressure with positional change.

Droxidopa is a synthetic amino acid precursor capable of crossing the blood-brain barrier, and is metabolized by aromatic L-amino acid decarboxylase into norepinephrine and epinephrine. It is a pressor outside the central nervous system in both neural and non-neural tissues. While it has been shown to be helpful for patients with neurodegenerative autonomic disorders, such as multiple system atrophy and Parkinson's disease, this is the first case report of its therapeutic use in NOH caused by CIN. While the main mechanism of action for both midodrine and droxidopa is activation of α_1 -adrenergic receptors, droxidopa can also increase cardiac ionotropic activity through the β_1 -adrenergic effects of norepinephrine.

Lundbeck database affirms there are no other cases of NOH/CIN treated successfully with Droxidopa thus far.

Acknowledgments

Funding: None

References

1. Figueroa J, Basford J, Low P. Preventing and treating orthostatic hypotension. As easy as A, B, C. *Cleve Clin J Med*. 2010; 77:298–306. [PubMed: 20439562]
2. Latronico N, Bertolini G, Guarneri B, Botteri M, Peli E, Andreoletti S, et al. Simplified electrophysiological evaluation of peripheral nerves in critically ill patients: The Italian multi-center CRIMYNE study. *Crit Care*. 2007; 11:R11. [PubMed: 17254336]
3. Visser LH. Critical illness polyneuropathy and myopathy: clinical features, risk factors, and prognosis. *Eur J Neurol*. 2006; 13:1203–1212. [PubMed: 17038033]
4. Bolton C1, Thompson J, Bernardi L, Voll C, Young B. The cardiac R-R variation and sympathetic skin response in the intensive care unit. *Can J Neurol Sci*. 2007; 34:313–5. [PubMed: 17803028]
5. Latronico N, Filosto M, Fagoni N, Gheza L, Guarneri B, et al. Small Nerve Fiber Pathology in Critical Illness. *PLoS ONE*. 2013; 8(9):e75696. [PubMed: 24098716]