Neuropathic orthostatic hypotension with critical illness neuropathy treated with droxidopa

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Abstract

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, 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 (Figueroa et al., 2010).

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 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 orthostasia, 145/89 mm Hg supine to 96/75 mm Hg 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 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 mm Hg supine to 90/60 mm Hg 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 mm Hg, DBP > 110 mm Hg) from multiple antihypotensives, 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 h while supine. At these doses, he maintained adequate standing blood pressure, despite ongoing orthostatic changes, with a decrease in blood pressure from 150/70 mm Hg supine to 90/60 mm Hg standing. He started to tolerate short walks, and over the course of the following week, his blood pressure further improved to 160/90 mm Hg supine to 117/73 mm Hg 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 (Latronico et al., 2007; Visser, 2006). 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 (Bolton et al., 2007; Latronico et al., 2013). 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 (Latronico et al., 2007). 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 α1-adrenergic receptors, droxidopa can also increase cardiac ionotropic activity through the β1-adrenergic effects of norepinephrine.

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

References


