Managing Orthostatic Hypotension in Parkinson’s Disease

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Hemodynamic Changes During Orthostasis

750-1,000 mL of blood is displaced downwards upon standing up

Several mechanisms in place to maintain orthostatic BP (baroreflex)

BP = blood pressure

Rowell LB. Human Circulation Regulation During Physical Stress. 1986.
Orthostatic Hypotension

A sustained fall of at least 20 mm Hg in SBP or 10 mm Hg in DBP within 3 minutes of standing or upright tilt

—AAS/AAN definition (2011)

SBP = systolic blood pressure
DBP = diastolic blood pressure

Orthostatic Hypotension

• Many causes of OH, including severe heart failure, adrenal insufficiency, dehydration, and severe anemia
  – Prevalence is high
    ▪ 5% in patients < 50 years old
    ▪ Increases with age
    ▪ Overall prevalence of OH in patients > 65 years is about 20%

OH = orthostatic hypotension

Orthostatic Hypotension

- It is a sign (not a symptom)
- Symptoms alone are not required nor sufficient to diagnose OH
- BP measurements in the supine and standing positions are required to diagnose OH
- Can be symptomatic or asymptomatic

Symptomatic Orthostatic Hypotension

• Typical well-known symptoms include:
  – Dizziness, lightheadedness, feeling about to faint when standing
  – Loss of consciousness (syncope)
  – Visual changes

• Less well-known symptoms include:
  – Coat-hanger pain
  – Shortness of breath
  – Angina
  – Cognitive slowing
  – Fatigue

Symptomatic Orthostatic Hypotension

MCA Velocity, cm/s

Vm: 55 cm/s

Vm: 28 cm/s

Vm: 46 cm/s

BP, mm Hg

120/85 mm Hg

68/55 mm Hg

95/62 mm Hg

MCA = middle cerebral artery
Vm = velocity

Two Types of Orthostatic Hypotension

- Non-Neurogenic
- Neurogenic
Non-Neurogenic Orthostatic Hypotension

• Very common in population > 65 years old

• Causes:
  – Anemia of unknown origin
  – Volume depletion
  – Heart failure
  – Significant varicose veins
  – Adrenal insufficiency

• Medications can cause or aggravate it
  – Diuretics
  – Antihypertensives
  – Nitrates
  – Sildenafil and others
  – Tricyclic antidepressants

Neurogenic Orthostatic Hypotension

• Disorder of noradrenergic neurotransmission resulting in deficient norepinephrine release from postganglionic sympathetic nerves

• Orphan condition affecting < 200,000 people in the United States
  – An estimated 30%-50% of patients with PD have nOH
  – nOH can be a feature of the premotor stage in patients with PD, DLB, and MSA

NE = norepinephrine
PD = Parkinson disease
DLB = dementia with Lewy bodies
MSA = multiple system atrophy

Neurogenic Orthostatic Hypotension Causes Significant Morbidity and Early Mortality

- Patients with PD and nOH are hospitalized more often, make more emergency department visits, and have earlier mortality than those with PD but without nOH
- Overall, the health-related cost among patients with PD and OH is 2.5 times higher than patients with PD without OH

Why Identifying Neurogenic Orthostatic Hypotension Is Important

• Early treatment could prevent serious morbidity that could be fatal
• nOH is the hallmark of neurologic disorders that affect sympathetic neurons
• nOH can be the first sign of a neurodegenerative disorder and predate cognitive and/or motor impairment

When to Suspect Orthostatic Hypotension

• Unexplained syncope/fall
• Typical symptoms (dizziness, lightheadedness, fatigue, confusion, gait disorders, neck pain, vision disturbance when standing)
• Patient’s history (age, neurodegenerative disease, diabetes, renal failure, amyloidosis, heart disease, hypertension, autoimmune disease)
• Patients on vasodilators, diuretics, alpha- and beta-blockers, tricyclic antidepressants

Patient complains of symptoms suggesting OH

- Dizziness
- Lightheadedness
- Feeling about to faint
- Syncope
- Blurry vision
- Shortness of breath
- Coat-hanger pain
- Weakness
- Fatigue

**UPON STANDING**

Measure BP and HR supine and after 3 min standing up

OH: 20/10 mm Hg

ΔHR/ΔSBP ratio

ECG, CBC, CMP, TSH, B₁₂

Autonomic testing (selected centers)

Non-Neurogenic OH

Neurogenic OH

CBC = complete blood count  CMP = comprehensive metabolic panel
TSH = thyroid-stimulating hormone  HR = heart rate

Ambulatory 24-Hour BP Monitoring

Hypertension when supine
Reversal of circadian rhythm

Symptomatic hypotension

BP, mm Hg

8 am

Management of Neurogenic Orthostatic Hypotension
Neurogenic Orthostatic Hypotension: Principles of Treatment

• Goal of treatment is to improve symptoms and quality of life—not to normalize BP

• Asymptomatic OH does not require pharmacologic treatment

Symptomatic OH 20/10-mm Hg fall in BP

Remove aggravating factors

Nonpharmacologic treatment

Reassess orthostatic BP and presence of symptoms

Consider pharmacologic treatment

Volume expansion (fludrocortisone)

Short-acting pressor agents (droxidopa, midodrine)

Nonpharmacologic Treatment

- Elevating the head of the bed 30-45 degrees with an electric bed/mattress
- Compression garments (binders/stockings)
- Increased fluid and salt intake:
  - Approximately 2 L of water daily
  - Patients with nOH who rapidly consume 500 mL of water can raise SBP by 30 mm Hg within 10-15 minutes
  - Liquids other than water do not provide the same BP response
  - It is recommended that nOH patients add 1-2 teaspoons of salt per day to their diet
- Physical conditioning
  - Lower-body strength training, moderate nonstrenuous activities
    - Stationary recumbent bicycle, rowing machine, water-based activities
    - Avoid upright exercises, treadmill, or running

Elevating the Head of the Bed Is the Most Effective Treatment

Dynamic Physical Exercise Lowers BP in Patients With Neurogenic Orthostatic Hypotension


*P < .05.
**P < .005.
***P < .0005.
Exercise in a Swimming Pool Prevents the Fall in BP

\[ \rho = \text{density of the fluid} \]
\[ g = \text{acceleration of gravity} \]
\[ h = \text{height of the column of fluid above the layer where pressure is being measured} \]

Rowell LB. Human Circulation Regulation During Physical Stress. 1986.
Physical Counter-Maneuvers to Prevent Orthostatic Hypotension

Breaking the Vicious Cycle of Orthostatic Hypotension

Intolerable symptoms on standing

Worsened fall in BP

Impaired cardiovascular control

Vicious Cycle of Physical Deconditioning

Physical inactivity

Striated and cardiac muscle atrophy

nOH

Pharmacology of Neurogenic Orthostatic Hypotension

AAAD = aromatic amino acid decarboxylase  
ACh = acetylcholine  
AChoE = acetylcholine esterase  
CNS = central nervous system  
NET = norepinephrine transporter  
NE = norepinephrine

2 FDA-Approved Drugs for Orthostatic Hypotension

• Direct sympathomimetic agent: midodrine
• Norepinephrine precursor: droxidopa
Midodrine

- FDA approval: 1996
- Selective alpha-1-adrenergic agonist
- Does not cross blood-brain barrier
- Predictable pressor effect ~1 hour post-administration
- Duration of action: ~3 hours
- Dosage: 2.5-10 mg up to 3 times/day
- Side effects:
  - Supine hypertension
  - Pilomotor reactions (goosebumps)
  - Urinary retention (rare)

Droxidopa

- FDA approval: 2014
  - First drug for nOH approved in 20 years
- Synthetic precursor of NE
- Predictable peak plasma concentration and pressor effect ~1 hour post-administration
- Duration of action: 4-6 hours
- Dosage: 100-600 mg 3 times/day

Cardiovascular Safety Considerations in the Pharmacologic Treatment of Neurogenic Orthostatic Hypotension

• All drugs for OH increase the risk of supine hypertension
• Patients should be instructed to avoid the flat position at all times and sleep with the head of the bed raised 30-45 degrees
• Some patients respond better to specific drugs (eg, patients with low NE levels respond well to droxidopa)
• Some patients require combinations of drugs
Clinical Management of Supine Hypertension in Patients With Neurogenic Orthostatic Hypotension

• Supine hypertension with droxidopa (> 160 mm Hg)
  – ~10% of patients
  – More common in those with higher baseline supine BP
  – Initial clinical management includes clinic and home BP monitoring with nonpharmacologic interventions (elevation of head of bed)

• Avoid dosing within 4 hours prior to bedtime
  – Physicians and patients should monitor supine BP as droxidopa dose is up-titrated
  – For more severe BP elevations, droxidopa can be down-titrated or discontinued
  – Short-acting antihypertensive agents can be administered at bedtime if necessary
Off-Label Use: Fludrocortisone

- Evidence-based data on fludrocortisone for nOH treatment are limited
- Increases renal sodium reabsorption, intravascular volume, and BP
- No more than 0.1-0.2 mg/day
- Long acting: clinical effects take 3-5 days to be noticeable (biological half-life is 36 hours)
- Side effects:
  - Hypokalemia and arrhythmia (short term)
  - Edema (short term)
  - Left ventricular hypertrophy and heart and renal failure (long term)
  - Increases risk of all-cause hospitalization in patients with OH

Off-Label: Pyridostigmine

- Acetylcholinesterase inhibitor
- Little effect as isolated drug
- Appears to enhance effect of other medications to increase sympathetic nerve activity in response to orthostatic stress
- Side effects: abdominal cramps, diarrhea, sialorrhea, excessive sweating, and urinary incontinence

Conclusion

• OH can be treated (if diagnosed)
• nOH has different pathophysiology and prognosis than non-neurogenic OH
• Treatment of OH starts with nonpharmacologic measures
• Pharmacologic treatment of OH includes midodrine, droxidopa, or fludrocortisone
• All patients must sleep with the head and torso raised 30-45 degrees