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Orthostatic hypotension: managing a difficult problem

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SUMMARY

Orthostatic hypotension (OH) leads to a significant number of hospitalizations each year, and is associated with significant morbidity and mortality among affected individuals. Given the increased risk for cardiovascular events and falls; it is important to identify the underlying etiology of OH and to choose appropriate therapeutic agents. Orthostatic hypotension can be non-neurogenic or neurogenic (arising from a central or peripheral lesion). The initial evaluation includes orthostatic vital signs, complete history and a physical. Patients should also be evaluated for concomitant symptoms of post-prandial hypotension and supine hypertension. Non-pharmacologic interventions are the first step for treatment of OH. The appropriate selection of medications can also help with symptomatic relief. This review highlights the pathophysiology, clinical features, diagnostic workup and treatment of patients with neurogenic OH.

Keywords

orthostatic hypotension; orthostatic intolerance; droxidopa; autonomic nervous system; autonomic failure; multiple system atrophy; Parkinson disease; peripheral neuropathy

INTRODUCTION

Increasing evidence has revealed that prolonged falls in blood pressure from orthostatic hypotension (OH) are a significant problem and may be an independent factor in increasing morbidity and mortality[1, 2] One recent meta-analysis found that OH increased the risk of all-

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cause mortality by 36% in affected individuals[2]. An additional analysis of patients in the Honolulu Heart Program found OH to be a significant, independent predictor of 4-year all cause mortality[3]. This was further supported by analysis of patients from the Atherosclerosis Risk in Communities study, which found that OH was predictive of mortality over 13 years of follow-up. In these patients, even after factors of age and comorbid conditions were factored in; patients with OH had a 1.7 fold increase in the risk of death[1]. Further studies have suggested that these patients are also at increased risk of coronary artery disease and heart failure[4]. Aside from these significant risks, patients with OH may also have a higher risk of recurrent falls[5] and decreased quality of life from untreated symptoms.

The prevalence of OH is around 18% in men and women aged 65 years and older[6]. It becomes more common with increasing age, with one geriatric clinic reporting 55% of patients over age 75 years are affected[7]. Not surprisingly, OH leads to a substantial number of hospitalizations each year; with one study reporting OH as the primary diagnosis in 35% of hospitalizations in the United States[8]. This number is only expected to grow with the increasing age of the population.

The emerging evidence that OH increases morbidity and mortality in patients and leads to a significant number of hospitalizations, underscores the importance of identifying an underlying cause of OH, mitigating any long-term sequelae and finding effective ways for treatment. This review will discuss the pathophysiology of orthostatic hypotension, review etiologies and diagnostic workup; and will also provide recommendations on therapeutic interventions.

THE PHYSIOLOGY OF STANDING

Upon assuming an upright posture from a supine or seated position, the cardiovascular system must promptly react to the increased effects of gravity. Between 500ml–1000ml of blood rapidly moves from the thorax and redistributes in the lower extremities and splanchnic vasculature[9]. Additionally, increased hydrostatic pressure in these tissues redistributes intravascular volume to the interstitium, resulting in approximately a 10% shift of plasma volume[10, 11].

Standing occurs as a result of the active contraction of abdominal and leg muscles to execute the movement and maintain posture and balance while upright. These muscle contractions act to compress the capacitance vessels and increase vascular resistance and blood pressure[12]. While this is useful for maintaining blood pressure while upright for a period of time, it in fact reduces blood pressure immediately upon standing. The muscular contraction causes a rise in intra-abdominal pressure and briefly increases venous return to the heart[13]. The low-pressure cardiopulmonary baroreceptors respond by decreasing sympathetic tone, which results in decreased vascular resistance and blood pressure. This phenomenon, combined with the added effects of gravity, results in a decline in venous return, stroke volume and subsequently arterial blood pressure.

The decline in blood pressure is immediately detected by both the high-pressure (carotid sinus and aortic arch) and low-pressure baroreceptors. These mechanoreceptors respond to

changes in pressure; a decline triggers a compensatory increase in sympathetic activity and withdrawal of parasympathetic activity. The net result is systemic peripheral vasoconstriction and a rise in heart rate to maintain blood pressure. Clinically, this can be observed by a 10–20 beat increase in heart rate, a 5 mmHg increase in diastolic blood pressure, and a minimal change in systolic blood pressure. Over time and depending on the degree of volume depletion, there is also neurohumoral activation through the renin-angiotensin-aldosterone system and vasopressin release that will also help maintain arterial blood pressure[14].

The autonomic nervous system plays a very important role to maintain homeostasis in response to changes in posture. Under normal circumstances, the autonomic nervous system has adequate “reserve” or ability to adjust blood pressure and heart rate, which allows adaptation and response to environmental changes. With damage to the autonomic nervous system (“autonomic failure”), the reserve may be depleted and inadequate. This can lead to upright OH, resulting in falls, pre-syncope and syncope.

DEFINING ORTHOSTATIC HYPOTENSION

Consensus Orthostatic Hypotension

Classically, OH is defined as a sustained or persistent fall in systolic blood pressure by 20 mm Hg or diastolic blood pressure of 10 mmHg within 3 minutes of standing or head up tilt[15] (Figure 1A). Patients with OH commonly present with complaints of lightheadedness with standing. They may report severe fatigue and feelings of presyncope or syncope. These patients may also report more nonspecific symptoms of headaches, neck or shoulder pain[16] (thought to be a result of ischemia to the neck musculature) orthostatic dyspnea[17] (secondary to inadequate perfusion of lung apices), confusion, somnolence with standing, nausea or generalized weakness. Although this definition of OH is the most commonly used, there are several variant forms that have also been identified.

Initial Orthostatic Hypotension

Initial OH is defined as a transient blood pressure fall (>40 mmHg systolic and/or >20 mm Hg diastolic blood pressure) within 15 seconds of standing that is associated symptoms of cerebral hypoperfusion (Figure 1B)[18]. The blood pressure usually recovers to normal in less than 1 minute. The initial decrease in blood pressure is thought to result from a mismatch between vascular resistance and cardiac output with active leg muscle contraction. One study found that 3.6% of patients presenting after a syncopal episode had a primary diagnosis of initial OH[18]. Patients may report symptoms of lightheadedness or syncope immediately after standing. Initial OH has a bimodal age distribution, with an early peak in adolescent patients [19] and another in middle age or older patients[20]. Initial OH can be more clinically pronounced in the setting of hypovolemia/dehydration or with the use of vasoactive medications.

In contrast to typical OH, the blood pressure fall is transient and initial OH is only seen with active standing (not in passive maneuvers as with tilt table testing). Continuous blood

pressure monitoring is usually required to document the blood pressure drops due to the slow time resolution of brachial cuff blood pressure assessments.

Delayed Orthostatic Hypotension

One variant of neurogenic OH is delayed OH. Delayed OH differs from classical OH in that the fall in systolic blood pressure by 20mm Hg or diastolic blood pressure of 10 mmHg occurs after the first three minutes of standing or head up tilt. An example of delayed OH is illustrated in Figure 1C.

One study of patients presenting with complaints of orthostatic intolerance found that 15% had blood pressure falls between 3 and 10 minutes and 39% had falls after 10 minutes[21]. Another study reported average time to symptom onset was about 8.6 minutes[22]. Patients with delayed OH were found to have less severe abnormalities of sympathetic adrenergic function, as compared to patients with neurogenic OH, suggesting a milder form of sympathetic adrenergic dysfunction. Additionally, patients with delayed OH were found to have progressive decrease in total peripheral resistance with the blood pressure fall, and no significant change in cardiac output or stroke volume when upright[22]. These same patients were found to have improvement in symptoms with lower limb compression stockings.

Distinguishing Delayed OH from Vasovagal Syncope

Both delayed OH and vasovagal syncope can cause blood pressure falls and can result in syncope, however these are very different disorders[23]. A key discriminating feature is the relative rate of blood pressure fall. In patients with vasovagal syncope, tilt table testing will reveal a sudden, rapid fall in blood pressure, often with an associated relative bradycardia and prodromal symptoms that could include diaphoresis, nausea, and a feeling of warmth. This sudden fall in blood pressure can occur several minutes after the table is tilted upright, in contrast to neurogenic OH where the fall in blood pressure occurs almost immediately on tilting the table upright. This is analogous to a rock rolling towards a cliff, and then suddenly falling off a cliff (Figure 2).

In contrast to vasovagal syncope, delayed OH is associated with a slow gradual decline in blood pressure, like a rock rolling down a hill (Figure 2). There is also typically a fall in heart rate with vasovagal syncope, which may accompany the fall in blood pressure. This is in contrast to delayed OH, where there is typically no decrease in heart rate. Patients with delayed OH may demonstrate additional abnormalities in sympathetic adrenergic function (see section on autonomic function testing), while this is usually normal in patients with vasovagal syncope.

CAUSES OF ORTHOSTATIC HYPOTENSION

Orthostatic hypotension can be classified as non-neurogenic or neurogenic. Non-neurogenic OH is typically caused by medications or clinical states that impair the autonomic nervous system or effective arterial blood volume. Common examples are illustrated in Table 1. Often, many of these causes are highly reversible and should be first considered when trying to correct symptomatic OH.

In contrast, neurogenic OH is caused by central or peripheral neurologic disease that results in autonomic dysfunction and a failure to correct for transient falls in blood pressure when standing through the mechanism described above. For the purposes of this review, we will focus primarily on neurogenic OH.

CAUSES OF NEUROGENIC ORTHOSTATIC HYPOTENSION

A peripheral or a central neurological lesion can cause neurogenic OH. Multiple system atrophy (MSA) is central disorder that causes progressive autonomic failure. Peripheral etiologies of neurogenic OH include pure autonomic failure (PAF), Parkinson's disease (PD), or any cause of peripheral neuropathy.

Multiple System Atrophy

MSA is a progressive neurodegenerative disorder caused by α-synuclein positive glial cytoplasmic inclusions in oligodendrocytes[24], in contrast to neuronal α-synuclein deposits in Lewy bodies. Autonomic failure primarily occurs from degeneration of pre-ganglionic autonomic neurons. MSA is a progressive disorder which can be further divided into MSA-C (cerebellar predominant) or MSA-P (parkinsonian predominant). In both subtypes, patients develop progressive degeneration of the autonomic nervous system with neurogenic OH, erectile dysfunction, urinary incontinence and constipation. Patients with MSA-C are noted to have more cerebellar dysfunction with ataxia and incoordination, while patients with MSA-P present with parkinsonian features of tremor and rigidity[25]. These patients may develop disordered breathing during sleep with obstructive sleep apnea, or laryngeal stridor. Nocturnal stridor has been linked to sleep-related laryngeal dystonia in some patients[26].

Since MSA is a central nervous system problem, patients with MSA have been noted to maintain intact post-ganglionic noradrenergic function, in contrast to Parkinson's disease and pure autonomic failure (discussed below), which display post-ganglionic denervation. This is illustrated by cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy scans in patients with MSA, where cardiac sympathetic neuronal uptake is intact which is consistent with a preganglionic lesion[27] (Figure 3). The prognosis is guarded in patients with MSA, with a median survival of ~8 years[28, 29] from onset of symptoms, although ranges from 4–15 years have been reported[24]. There are currently no proven therapies to alter the course of MSA, so the treatment is largely symptomatic.

Parkinson's disease

PD is characterized by resting tremor, bradykinesia, rigidity and postural instability. The prevalence of neurogenic OH ranges from 20–60% percent in patients with PD[30, 31] and typically occurs later in the disease course. However, one study found that only 16% of patients with PD and neurogenic OH were symptomatic.[32] The distinction between MSA and PD is often made through clinical exam. Classically, patients with PD are noted to have significant improvement with levodopa with later onset of OH; while patients with MSA will not typically respond to levodopa and autonomic symptoms are present early. This distinction, however, can sometimes be difficult to discern, and requires serial exams to assess for disease progression.

Dementia with Lewy bodies

Dementia with Lewy bodies is characterized by dementia, parkinsonism, visual hallucinations, cognitive fluctuations and autonomic dysfunction. The disorder is often more rapidly progressive than PD, and these patients have been noted to have more severe OH as compared to PD patients[33]. Symptomatic OH has been reported in 30–50% of cases[24].

Pure Autonomic Failure

PAF, previously called “idiopathic OH”, is characterized by isolated peripheral autonomic failure with neurogenic OH. Just as in patients with MSA, PD and LBD, these patients may also present with symptoms of diffuse autonomic involvement with GI, urinary and sudomotor abnormalities. Patients with PAF have also been found to have diminished renal function secondary to supine hypertension[34].

As noted earlier, cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy has revealed decreased uptake of MIBG in patients with PAF and PD (Figure 3), supporting the pathophysiology of a postganglionic sympathetic nervous system lesion[27, 35]. Some patients may present early with what appears consistent with PAF, but over time the clinical picture may be more consistent with PD[36] or MSA.

Peripheral Neuropathies

Small and large fiber neuropathies can lead to neurogenic OH. The most common cause of neuropathy in our patient population is diabetes mellitus. Additional causes of neuropathy include amyloidosis and immune mediated or hereditary neuropathies. Vitamin deficiencies such as low vitamin B_{12} can lead to and orthostatic hypotension which may improve with vitamin supplementation[37]. Exposure to heavy metals, certain medications (chemotherapy agents), and infectious diseases such as HIV can also cause neuropathy. Autonomic failure that presents in an acute or subacute setting may warrant consideration of a possible autoimmune or paraneoplastic etiology (autoimmune autonomic ganglionopathy [AAG]).

Clinical Evaluation of Orthostatic Hypotension

History

The initial evaluation of patients with suspected OH begins with a thorough history. Clinicians should look for signs of autonomic failure; such as a patient’s report of lightheadedness with standing, urinary incontinence, severe constipation, sweating abnormalities, inability to eat a large meal (suggestive of gastroparesis), or numbness and tingling of the extremities (suggestive of a peripheral neuropathy). Cognitive problems with standing have been reported in about 50% of patients over the age of 60 with OH[38]. Additional pertinent elements of the history include features of a parkinsonian syndrome such as resting tremor, falls, visual hallucinations, symptoms of rapid eye movement (REM) behavioral sleep disorder, decreased sense of smell or rigidity.

After obtaining a detailed history, the patient’s medication list should be carefully reviewed. It is important to determine if symptoms may be secondary to medication induced falls in blood pressure. Any medications which can lower the blood pressure such as diuretics,

venodilators, alpha antagonists (including benign prostatic hypertrophy medications) or vasodilators could potentially be contributing to blood pressure falls, and the necessity of these medications should be considered (TABLE 1).

Physical Examination

The physical exam may provide additional clues, as to the cause of OH. The exam should include measurement of orthostatic vital signs, a skin evaluation to look for sympathetic cholinergic changes causing dryness and a neurologic exam to evaluate for parkinsonian features or signs of a peripheral neuropathy.

Orthostatic Vital Signs

To obtain accurate blood pressure recordings, a supine blood pressure and heart rate measurement is obtained after the patient has been supine for several minutes (TABLE 2). This is to ensure fluid equilibration has occurred after a change in body position to the supine position. The patient is then instructed to stand up. The blood pressure and heart rate are recorded after 1 minute, 3 minutes and ideally 5 minutes of standing. While the 5-minute recording is not absolutely required to make the diagnosis of OH, it can provide information as to whether the blood pressure continues to fall with time or plateaus[39]. Notation should be made of any symptoms that the patient experiences upon standing.

Laboratory Evaluation

Further evaluation with blood work may help to reveal any underlying cause of the autonomic failure. For example, in patients with an exam consistent with a length dependent peripheral neuropathy, screening blood work for potential causes of neuropathy is obtained. In our patient population, type II diabetes mellitus is the most common cause of neurogenic OH and peripheral neuropathy. Typically blood work begins with a Hga1c to diagnose diabetes mellitus. Additional tests include a serum and urine protein electrophoresis to evaluate for a paraproteinemia (usually caused by an underlying immunoproliferative disorder, ANA survey to screen for inflammatory diseases and vitamin B_{12} levels. A complete blood count (CBC) may also be helpful to evaluate for any underlying anemia which may be exacerbating symptoms. If autonomic failure presents in an acute or subacute in manner, ganglionic nicotinic acetylcholine receptor antibodies or paraneoplastic antibodies may also be drawn.

Plasma Catecholamine Levels

Supine and standing plasma catecholamines may also be helpful. Norepinephrine (NE) is the primary neurotransmitter in the vascular sympathetic nervous system. If allowed to reach steady state in a set body position, and in the absence of an acute adrenal discharge, the plasma NE can be used as a surrogate for sympathoneural activity. In PAF, plasma NE levels are low when supine, with little increase upon standing. In contrast, MSA patients often have normal plasma NE levels while supine, but a blunted increase on standing, compared to healthy subjects[31]. There is considerable overlap in catecholamine levels in patients with MSA and PD, which highlights the need for development of additional diagnostic biomarkers.

For accurate catecholamine samples, patients must be in a relaxed, supine position when blood is drawn; then they stand for at least 5 minutes (to allow for steady-state levels) before another sample is drawn. If the patient cannot stand for the entire duration due to orthostatic symptoms, then they can sit briefly, but should not return to the supine position.

Autonomic Cardiovascular Testing

Autonomic function testing can provide further assessment of parasympathetic and sympathetic adrenergic function. This testing is performed at specialized centers and may be helpful for further evaluation of patients with neurogenic OH. Autonomic function testing is particularly useful in patients who are unable to safely stand in clinic for assessment of blood pressure. The tilt table test can help characterize OH by revealing the onset, duration and magnitude of blood pressure falls. It is also particularly useful if there is concern for delayed OH, which may not be easily captured in bedside assessments.

Autonomic testing is performed in a quiet, temperature controlled room. Patients are placed on continuous blood pressure and heart rate monitoring. Cardiovagal function is evaluated through analysis of the heart rate response to deep breathing. During this test, patients are instructed to maximally inhale for 5 seconds and then exhale for 5 seconds. This is repeated for around 6 to 8 cycles. The difference between the end of inspiration and end of expiration heart rates are analyzed and compared to normative data based on age and gender. The sinus arrhythmia ratio, heart rate in expiration divided by the heart rate in inspiration, is also used as a marker of cardiovagal tone (with higher values indicating more robust cardiovagal tone). Decreased heart rate variability is reflective of parasympathetic dysfunction. An additional measure of parasympathetic function is the heart rate response to a Valsalva maneuver. For this maneuver, patients are instructed to exhale against a resistance of about 30–40 mm Hg for 15 seconds. A Valsalva ratio is derived from the maximum heart rate during the expiratory phase, over the minimum heart rate during the relaxation phase. An adequate blood pressure response is required to drive the changes in heart rate. A reduction in the Valsalva ratio is also suggestive of parasympathetic dysfunction.

Sympathetic adrenergic function can be evaluated through the blood pressure response to the Valsalva maneuver. There are characteristic changes in blood pressure during and after expiration. Any abnormality in the blood pressure analysis may be reflective of sympathetic adrenergic failure[40, 41].

The tilt table test is another way to evaluate the sympathetic adrenergic system. It is performed after the patient has been lying supine for at least 20 minutes. Baseline blood pressure and heart rate recordings are documented. Then the table is rapidly tilted up to 60–80 degrees. Although there are differing protocols for tilt table tests among centers, a standardized procedure should be followed. Some testing centers may use provocative medications (nitroglycerine, isoproterenol) to increase the likelihood of an abnormal test. However, these medications are typically not needed in patients with neurogenic orthostatic hypotension, may reduce the specificity of the study and may produce confounding effects from the medication[42, 43]. A prolonged head-up tilt of 20–30 mins usually required to capture any delayed falls in blood pressure. Examples of tilt table abnormalities are illustrated in FIGURE 1.

SPECIAL CONSIDERATIONS IN PATIENT WITH NEUROGENIC OH

Post-prandial Hypotension

In patients with autonomic dysfunction 40%–80% of patients will have post-prandial hypotension[44]. This is commonly defined as a decline in systolic arterial pressure of 20 mmHg or a systolic arterial pressure less than 90 mmHg (with a pre-meal systolic arterial pressure greater than 100), within 2 hours of consuming a meal[45]. Some patients describe episodes of fainting into their plates while out at a restaurant with their families. Ambulatory blood pressure monitoring can aid in the diagnosis of post prandial hypotension. Studies in patients with autonomic failure have revealed that blood pressures falls occur within 10–15 minutes of food ingestion, and reach a nadir around 60 minutes[46]. One study found that meal composition can determine the degree of blood pressure fall. Meals with higher glucose load were found to lower blood pressure more significantly than meals with higher fat content. Higher protein content was associated with the least amount of blood pressure change, when compared to a high glucose or lipid meal[46].

Supine Hypertension

Supine hypertension (HTN) is seen in patients with both peripheral and central autonomic failure. We previously found that approximately 60% of our patients with neurogenic OH had supine hypertension[23] (Figure 1D). The degree of hypertension has been correlated with the severity of OH[47]. Supine hypertension should be assessed during each clinic visit. Patients are instructed to lay flat for several minutes and blood pressure is recorded. Outpatient monitoring can also be helpful with use of 24 hour blood pressure monitors. Special notation should be made of any hypertensive nighttime recordings, which may be from elevated blood pressures while sleeping.

Medications used to treat OH can sometimes exacerbate supine HTN, but most patients with supine hypertension will have high supine blood pressures even in the absence of contributory medications. It is important to note that the presence of supine hypertension has therapeutic and symptomatic implications. Persistent elevations in supine blood pressure may limit the dose escalation of some pressor agents, and may contribute to a nocturnal pressure natriuresis, which can lead to severe morning OH. Additionally, if left unaddressed, patients may develop subsequent end organ damage with left ventricular hypertrophy and renal dysfunction[48].

TREATMENT OF ORTHOSTATIC HYPOTENSION

Treatment of OH begins with patient education and a trial of non-pharmacological interventions (Table 3). The focus is not necessarily to treat the actual blood pressure measurements (as an end in itself) or modify the disease course. Rather, the goal of treatment is to decrease symptoms, improve quality of life and prevent complications such as falls and supine hypertension.

Patient Education

Clinicians should review situations which may exacerbate symptoms, such worsening lightheadedness in the morning from nocturnal diuresis[49], or in warm environments (such as after hot showers or on summer days) which may result in heat-induced peripheral vasodilation. It is helpful to discuss the prodromal symptoms of syncope and to teach patients maneuvers that can help reduce venous pooling[50]. We advise patients to check their blood pressures intermittently. Patients are advised to lie down and record their supine heart rate and blood pressure, then to stand up and to record heart rates and blood pressures and 1-min, 3-min and 5-min.

Non-pharmacologic treatments

Non-pharmacologic treatments include increasing fluid intake, up to 2–3 liters per day. The goal is to increase fluid retention and subsequently increase intravascular blood volume. Patients are also advised to increase salt intake (6–9 grams per day) [51]. This can be achieved through increasing dietary salt or by using over the counter salt tablets.

Osmopressor Response—In addition to increasing fluid intake throughout the day; rapid ingestion of water may also help to raise blood pressure. Vanderbilt University investigators first reported that rapid ingestion of approximately 500 mL of water by patients with neurogenic OH and autonomic failure increases systolic blood pressure (>40 mm Hg on average)[52, 53]. This pressor response takes 5–10 min to start, peaks between 20 and 40 min post-ingestion, and starts to dissipate by 60 min. In effect, it has the time line of a very short acting medication.

The pressor response relates to the oral ingestion, and not primarily to blood volume expansion. The pressor response was much greater with 500 ml of oral water than when 500 mL of 5% dextrose in water (D5W) was given intravenously in the same patients[53]. Salt water (0.45% saline) induced only 50% of the pressor response compared with plain water. This suggests that the key to the response is the Seinfeld Effect – the “nothingness” (or hypo-osmolality) of the water[54]. More detailed animal experiments have documented that this reaction can be produced with duodenal infusions, that it induces an increase plasma NE, and that the pressor effect can be blocked with an alpha-antagonist[55]. Taken together, these data suggest that this is an osmolality-induced response (“osmopressor response”) that engages residual sympathetic nerve activity. From a practical viewpoint, the authors advise their patients to drink 500 mL of water rapidly (within 2–3 minutes) first thing in the morning, and later in the day as needed for a brief blood pressure boost.

Abdominal Binders and Compression Stockings—The use of abdominal binders have also been found to increase systolic blood pressure by about 11mmHg[56]. To be effective, the binders need to be tightly fitted. It may be challenging for patients to generate adequate tightness themselves, so a second person is often needed to put the binder on. Compression stockings, ideally waist-high (pantyhose style), which are custom fitted may also be helpful to prevent blood pooling in the lower extremities. However, abdominal compression is critically important, given that the lower abdomen and pelvis may harbor 20% to 30% of total blood volume[56]. As with abdominal binders, patients may report

difficulty getting compression stockings on, which can limit compliance. In these cases, a family member or caregiver may be required to assist them.

Sleeping with the head of the bed elevated may also be helpful. This is discussed in more detail in the section below on the treatment of Supine Hypertension.

Pharmacologic Treatments

There are several medications to help alleviate the symptoms of OH (Table 4). These are typically used when patients fail non-pharmaceutical treatments, or when symptoms are very severe and can be used in conjunction the strategies discussed above.

Midodrine—Midodrine was the first USA Food and Drug Administration (FDA) approved medication for OH. It is a pro-drug which is rapidly converted to its active metabolite, desglymidodrine. Desglymidodrine is a selective α1-adrenergic agonist with a short half-life, and duration of action of about 3–4 hours. Midodrine has been shown to significantly increase standing blood pressures while decreasing symptoms of orthostatic intolerance[38, 57, 58]. A recent meta-analysis also concluded that midodrine improves clinical outcomes with minimal serious side effects[59]. The dose typically starts at 2.5 mg per dose, and can be increased up to 10–15 mg per dose. Given the short half-life, a typical dosing schedule is every 4 hours when upright starting in the morning (e.g. 8am, noon, 4pm). It should NOT be given at bedtime, and patients should avoid lying down for 4–5 hours after the last dose of midodrine, to avoid worsening supine hypertension. Given it short half-life, it can also be used on an as needed (PRN) basis prior to specific activities that bring on symptomatic orthostatic hypotension. The side effects of midodrine include supine hypertension; piloerection (goose bumps), scalp tingling (which is often tolerable if a patient knows to expect this side effect), urinary urgency or retention, and rarely headaches.

Fludrocortisone—Fludrocortisone is a synthetic mineralocorticoid that increases intravascular volume and renal sodium reabsorption. The starting dose is typically 0.05mg daily and can be increased up to 0.2 mg (in a single or split dose). Side effects may include hypokalemia, headaches, peripheral edema, heart failure and supine hypertension. At higher doses, patients may be at increased risk of hypothalamic-pituitary-adrenal axis suppression. In one study, ~30% of patients stopped taking fludrocortisone due to side effects[60]. In a patient with pre-existing supine hypertension, fludrocortisone is typically not chosen as a first line medication, and midodrine may be more appropriate.

Pyridostigmine—Pyridostigmine is an acetylcholinesterase inhibitor that is marketed for the treatment of myasthenia gravis. It has been shown to increase standing blood pressures by inhibiting acetylcholinesterase and thus enhancing sympathetic ganglionic transmission[61]. The typical starting dose is 30 mg. Side effects include abdominal discomfort and urinary urgency[61]. In theory this medication does not cause significant supine hypertension, as seen in other medications for OH. This is because ganglionic transmission is minimal when supine and increases when standing[61]. However, the effect on increasing blood pressure is mild and may not be entirely effective in alleviating symptoms from severe OH[62].

Droxidopa—Droxidopa is a synthetic precursor of NE that is converted to NE by aromatic L-amino acid decarboxylase. The FDA has recently approved droxidopa in 2014 for the treatment of neurogenic orthostatic hypotension. This medication increases circulating levels of NE, which leads to increased adrenergic receptor stimulation. Droxidopa acts at the neurovascular junction and raises blood pressure by increasing vascular tone.[63] In recent studies droxidopa was found to significantly increase standing systolic blood pressures and improve patient reported symptoms[64]. The starting dose is 100mg three times daily, and may be titrated up to a maximum daily dose of 1800mg. The main side effect of this medication is supine hypertension, and there is a black box warning on the medication due to this. However, supine hypertension can and should be monitored in all patients and mitigated through strategies previously discussed.

Additional Off Label Agents

Atomoxetine—Atomoxetine is a NE transporter inhibitor, which is approved for the treatment of attention deficit hyperactivity disorder (ADHD). However in patients with autonomic failure from MSA who demonstrate intact peripheral noradrenergic function, this medication can cause a potent peripheral vasoconstriction which is unopposed and leads to an increase in blood pressure[65]. This medication can exert a pressor effect in PAF, but it is not as effective in patients with MSA, since the peripheral noradrenergic system is impaired in PAF. One study found that atomoxetine produced a greater pressor response in upright blood pressures as compared to midodrine, and also improved reported OH symptoms as compared to placebo[66], with upright blood pressure increased by 50 mmHg[67] with use of atomoxetine. Although atomoxetine is “off-label” for OH, it may be useful in patients with refractory or debilitating OH symptoms. Patients are advised to use the medication at least 60 minutes prior to standing and avoid the supine position for about 4 hours after ingestion.

Octreotide—Octreotide is a synthetic somatostatin analogue peptide that causes constriction of the splanchnic circulation and reduces venous pooling. Octreotide has been shown to delay the time of blood pressure fall with upright tilt in a group of patients with MSA[68]. However, this medication has limited utility due to parenteral administration and side effects of diarrhea, abdominal pain and hyperglycemia.

Yohimbine—Yohimbine is an α-2 adrenergic receptor antagonist has been shown to increase standing blood pressure by removing inhibition of NE release from the pre-synaptic sympathetic neuron[69]. Pharmacologically, it is effectively the “anti-clonidine”. Yohimbine has been found to be more effective in improving standing blood pressures and patient symptoms OH, as compared to pyridostigmine[70]. While yohimbine is still FDA approved (for erectile dysfunction), it is no longer commercially manufactured so a compounding pharmacy is required to obtain this medication.

Pseudoephedrine—Pseudoephedrine**,** a stereoisomer of ephedrine, is a mixed alpha-adrenergic agonist, which stimulates α, β1, and β2 receptors, and is sold as an over the counter decongestant. Studies have shown that ephedrine is less effective than midodrine in raising blood pressure in patients with autonomic failure[71]. This may be due to ephedrine’s activity on β1 and β2 receptors, as compared to midodrine (which does not affect beta

receptors). Additionally, one study found that the combination of pseudoephedrine 30 mg and water substantially increased blood pressure by around 52 mmHg in patients with severe OH[52].

Ergotamine—Ergotamine causes peripheral vasoconstriction through stimulation of α-adrenergic receptors and is another medication that has been evaluated for treatment of orthostatic hypotension. One study evaluating inhaled ergotamine tartrate demonstrated a significant increase in upright blood pressure 2 hours after inhalation when compared to placebo. These patients had no side effects; however none of the participants had coronary or peripheral artery disease[72]. Several important side effects have been noted which include vasospasm or vasoconstriction, also reported with chronic use is valvular heart disease. The vasospasm may involve peripheral limb arteries and have been reported to cause gangrene. Given such, this medication is not routinely recommended and is contraindicated in patients with underlying vascular disease.

Caffeine—One open label study evaluating caffeine with ergotamine found improvement in standing blood pressure and presyncopal symptoms in patients with autonomic failure[73]. An additional randomized single blind cross-over study found that the combination of ergotamine and caffeine increased seated systolic blood pressure, and while there was no significant effect of this combination on orthostatic intolerance; patients did have improved presyncopal symptoms with standing[74].

Recombinant Erythropoietin—Many patients with autonomic failure have co-existent anemia. Recombinant erythropoietin has been used to raise blood pressure in patients with orthostatic hypotension.[75, 76] It will also raise supine blood pressures in susceptible patients, making its use unadvisable in patients with co-existent supine hypertension.

Treatment of Post-Prandial Hypotension

The initial treatment approach to postprandial hypotension is non-pharmacological. Patients with post-prandial hypotension should be advised to take in smaller more frequent meals. The goal of this is not to calorie restrict, but to limit the food load at any given time. If this is not adequate, then patients should be instructed to decrease the carbohydrate load in their diet. While the non-pharmacological approaches are usually adequate, sometimes medications are also required. One study found that acarbose, a glucosidase inhibitor which decreases glucose absorption in the small intestine, significantly attenuated the fall in blood pressure after eating in patients with post-prandial hypotension[77]. However common side effects of this medication include diarrhea, abdominal cramping and bloating, which may limit utility. Another pharmacological alternative is octreotide, although as a peptide, this requires subcutaneous injections.

Treatment of Supine Hypertension

Treatment of supine hypertension during the day can be accomplished by instructing patients to avoid lying down, and to remain upright or recline in a chair (if a nap is needed). At night, one conservative approach includes raising the head of the bed by 6–9 inches. This can be accomplished by putting wood or concrete blocks under the headboard or by using a foam

wedge under the mattress. Using numerous pillows will contort the patient, but it will not achieve the desired result.

Given that these patients can often experience hypotension with carbohydrate intake, another approach to treating the supine hypertension is to ask these patients to have a sweet desert immediately before bedtime. Additionally, patients are advised to use a bedside commode to limit falls at night. These falls are often associated with nocturnal trips to the bathroom due to concomitant neurogenic bladder. There are no medications approved for the treatment of supine hypertension, but there are several potentially useful agents. Nitroglycerin patches can be applied at bedtime and easily removed in the morning. Often only a low dose is required (0.1–0.2 mg/hr) since these patients are blood volume dependent, and very sensitive to the venodilatory effects of nitrates. Potential oral medications include hydralazine 25–50 mg, minoxidil, sildenafil or short-acting nifedipine[78]. One study found that oral losartan 50 mg taken at bedtime, reduced supine blood pressure, did not worsen morning OH, and decreased nocturnal urinary sodium excretion. This was in comparison to captopril which also did not worsen morning symptoms; however had little effect on supine blood pressure[79].

References

Reference annotations

* Of interest

** Of considerable interest

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EXPERT COMMENTARY

The initial evaluation of patients presenting with symptoms of orthostatic intolerance involves a focused history investigating the timing of symptoms, provoking factors, and associated complaints such as tremor, paresthesias, sweating abnormalities or genitourinary and gastrointestinal symptoms. Further workup should be focused on localizing the cause of autonomic dysfunction. In select cases, as in some peripheral neuropathies, early identification and modification of causative factors can help prevent further autonomic degeneration.

The main goals in treatment of OH are to reduce disabling symptoms and improve quality of life. Given the growing evidence that OH leads to increased morbidity and mortality—clinicians should be diligent in optimizing treatment. This begins with educating patients on the basic mechanisms of OH, providing counseling on strategies to avoid triggers, and instructing patients on ways to increase salt and fluid while monitoring blood pressures. When these measures fail or are not sufficient, medications may be carefully selected and titrated. The main pharmaceutical treatments of neurogenic OH had been fludrocortisone and midodrine. However, the approval of droxidopa has expanded the arsenal of therapeutic strategies in treating patients with neurogenic OH. In many cases medications can work in conjunction with non-pharmaceutical strategies to decrease subjective symptoms and reduce long-term complications.

FIVE-YEAR VIEW

The increasing evidence that OH leads to a high risk of morbidity and mortality, underscores the need for clinicians to accurately diagnose and treat the underlying condition. The prevalence of OH, and hospitalizations due to OH both increase with advancing age. Given the aging of Western populations, these data suggest that OH will become a more common clinical problem over the next few years. The results will be an increase in both medical costs at a systems level, and an increase in morbidity at a personal level. There are currently only 2 drugs approved by the FDA for orthostatic hypotension (droxidopa and midodrine), and the FDA has called for hearings to advise whether midodrine should be withdrawn from the US market[80]. There is a lack of large, high quality studies to guide our management of OH. Such studies are needed to provide clinicians with the tools to provide the best care to their patients.

KEY ISSUES

- Orthostatic hypotension (OH) is a common cause of hospitalizations, particularly among the elderly and leads to significant morbidity and mortality when untreated
- Patients with OH have increased risk of cardiovascular complications, including increased coronary artery disease, stroke and heart failure
- Orthostatic hypotension can be classified as non-neurogenic (from medications or volume depletion) or neurogenic OH (from multiple system atrophy, Parkinson's disease, Lewy body dementia or pure autonomic failure)
- Evaluation of these patients includes complete history and physical exam, detailed orthostatic vital signs and autonomic function testing
- Patients with OH also may develop supine hypertension and post-prandial hypotension which should properly evaluated and treated to prevent complications
- Non-pharmacological interventions, including patient education on the causes & triggers of orthostatic hypotension, and are first line in the treatment of OH
- Medications such as midodrine, fludrocortisone, droxidopa and pyridostigmine may provide additional symptomatic benefit to patients
- High quality studies of optimal treatments of OH are desperately needed

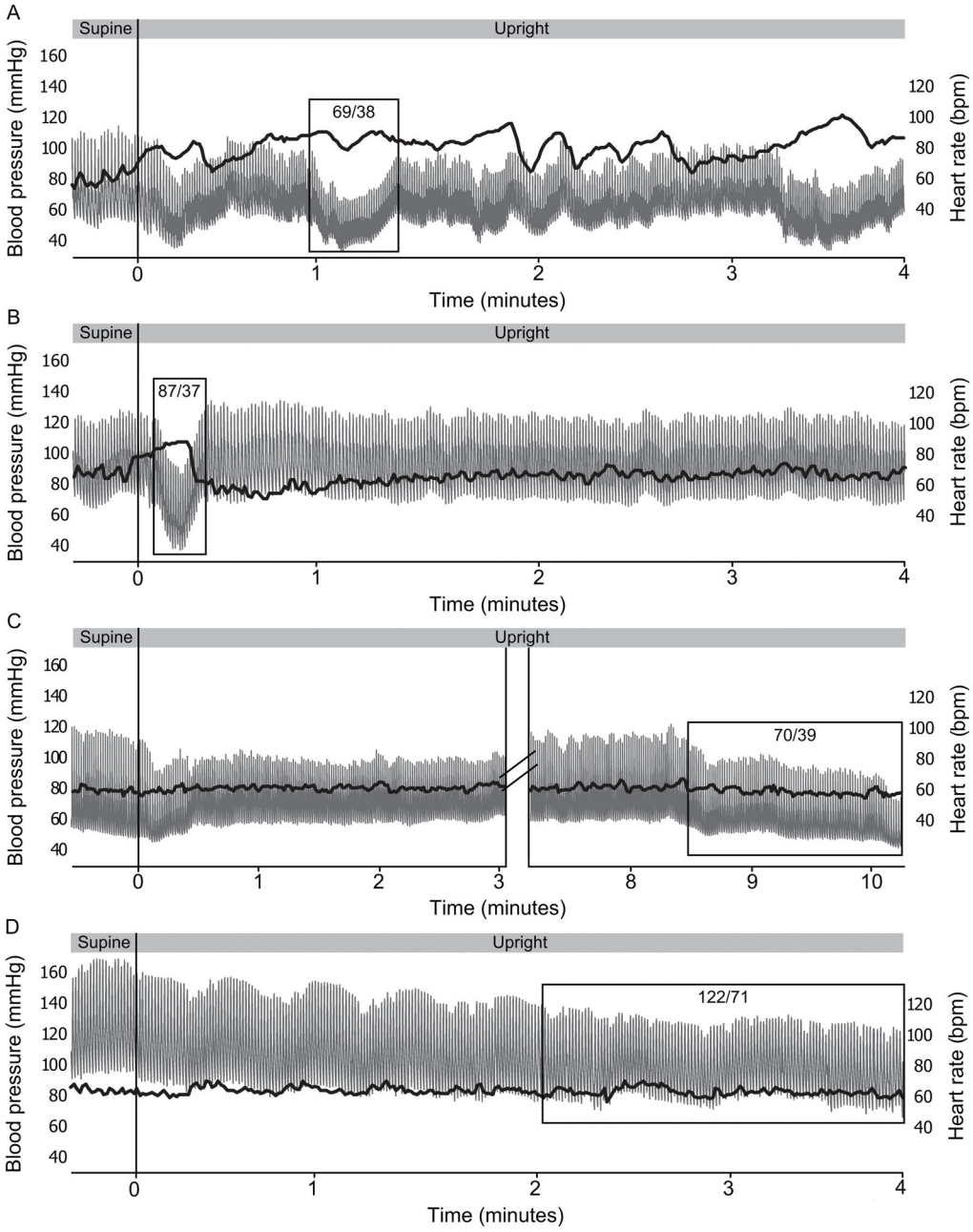

FIG. 1. Examples of Tilt table abnormalities

Panel A is an example of classic neurogenic orthostatic hypotension, during which there is fall in blood pressure within the first 3 minutes of assuming upright posture. Panel B demonstrates initial OH, with a sudden, transient decrease in blood pressure with the upright position, and subsequent recovery. Panel C is an example of delayed orthostatic hypotension, in which the fall in blood pressure occurs after 3 minutes. Panel D is an example of classic orthostatic hypotension in the setting of supine hypertension. Reproduced with permission from Springer Science + Business Media: Clinical Autonomic Research, The relationship

between orthostatic hypotension and falling in older adults, 24, 2013, Shaw BH & Claydon VE.

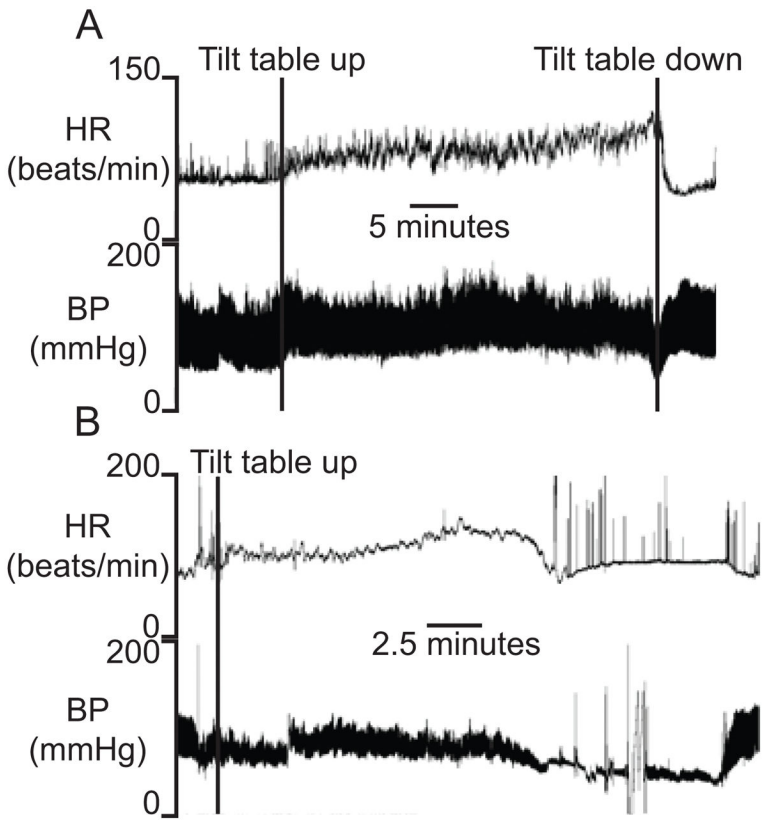

FIG. 2. Distinguishing Vasovagal syncope from Delayed OH

Panel A demonstrates vasovagal syncope. The patient maintains blood pressure and heart rate with upright tilt. After prolonged tilt; there is a sudden, precipitous fall in blood pressure and heart rate. The BP fall was if a boulder fell off of a cliff. Panel B shows a patient with delayed orthostatic hypotension. Note the gradual and progressive fall in blood pressure with head-up tilt that eventually drops to a significant degree. The BP was akin to a boulder rolling down a hill. Reprinted from Electrophysiological Disorders of the Heart, Sanjeev Saksena, Robert S. Sheldon, 985–995, Copyright (2012), with permission from Elsevier.

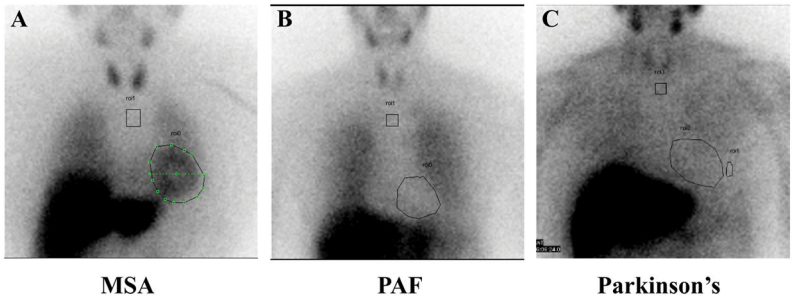

FIG. 3. Cardiac ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy scans in patients with Multiple System atrophy (MSA), pure autonomic failure (PAF) and Parkinson's disease (PD)

MIBG is taken up by intact postganglionic sympathetic neurons. Note that in MSA (Panel A), a "central" autonomic disorder, the cardiac MIBG intake is normal, which is consistent with a preganglionic lesion. In contrast, in PAF (Panel B), a "peripheral" autonomic disorder, and PD (C), cardiac MIBG uptake is decreased, which is reflective of a postganglionic lesion. PD (Panel C) has a cardiac MIBG pattern similar to PAF, suggesting that the autonomic failure in PD is also a "peripheral " autonomic disorder. Reprinted from Cardiology Clinics, Victor C. Nwazue, Satish R. Raj, Confounders of Vasovagal Syncope Orthostatic Hypotension, 89–100, Copyright (2013), with permission from Elsevier.

Table 1

Common Causes of Non-neurogenic Orthostatic Hypotension

Medications
Diuretics: thiazides, furosemide
Venodilators: nitrates
Direct vasodilators: hydralazine, amlodipine, nifedipine, alpha antagonists (terazosin, tamsulosin)
Anti-depressants: amitriptyline, nortriptyline
Clinical states
Hypovolemia: dehydration, bleeding
Impaired cardiac output: cardiac arrhythmias, aortic stenosis, heart failure
Venous pooling: fever

Table 2

How to Measure Orthostatic Vital Signs

Correct measurement of Orthostatic Vital Signs
1. Obtain supine blood pressure and heart rate measurement after laying down for 1–2 minutes
2. Then stand up (do not inflate cuff immediately) • Record both the blood pressure (BP) and heart rate (HR) at minute 1 • Record BP and HR at minute 3 • Record BP and HR at minute 5
3. Record any symptoms occurring with standing and time of day
4. If patients are unable to stand for the full amount of time, a sitting measurement can be taken, however they should not return to the supine position.

Table 3

Non-Pharmacological Treatments for Orthostatic Hypotension

Non-Pharmacological Treatment for OH	
Increase fluid intake	Patients are advised to increase fluid to a target of 2–3 liters per day
Increase dietary sodium	Increase sodium intake up to 10 grams per day
Oral water bolus (Osmopressor Response)	Drinking 500 mL of water within 2–3 minutes can effectively increase blood pressure, the effect peaks between 20–40 minutes after ingestion
Raise the head of the bed	Elevated head by 6–9 inches, use wood/concrete blocks under headboard a foam wedge under the mattress
Compression garments	Promote use of abdominal binders and/or waist high compression stockings (start with 30–40 mm Hg)
Review physical counter maneuvers	Leg crossing and squatting, may help to prevent syncope

Table 4

Medications for the treatment of Neurogenic Orthostatic Hypotension

Medication	Dose	Adverse Effects	Comments
Midodrine	2.5–10 mg PO q4H; or PRN	Supine HTN, piloerection, urinary retention, scalp tingling	Do not take 4 hours prior to bedtime
Fludrocortisone	0.05–0.2 mg PO daily	Supine HTN, headache, hypokalemia, edema	Monitor potassium when on medication
Droxidopa	100 mg TID up to total daily dose 1800 mg	Supine HTN	Monitor for supine HTN
Pyridostigmine	30–60 mg PO TID	Excessive salivation, abdominal cramping, nausea/vomiting	May help with constipation, maximally effective when upright
Yohimbine	5.4–10.8 mg PO TID	Irritability, hypertension, anxiety	Not widely available, obtain through compounding pharmacy
Atomoxetine	18–40 mg PO BID	Headache, insomnia	Off-label and often expensive; most effective in central forms of OH
Octreotide	12.5–50 microgm SQ BID	Severe seated hypertension	Requires refrigeration and daily injections
Pseudoephedrine	30–60 mg PO TID	Supine HTN, central sympathomimetic effects (anxiety, tremor), rare cases of intracerebral hemorrhage, vasculitis	Do not take 4 hours prior to bedtime
Caffeine/ergotamine	100 mg/1mg tablet PO BID	Supine HTN, high doses of ergotamine with reported cardiac valvular abnormalities and severe vasospasm	Avoid in patients with history of cardiac disease

Abbreviations: PO - orally; q4H - every four hours; PRN - as needed; HTN - hypertension; OH – orthostatic hypotension; TID - three times a day; SQ - subcutaneously; BID - twice a day.