Management of neurogenic orthostatic hypotension: an update

Phillip A Low, Wolfgang Singer

Orthostatic hypotension (OH) is common in elderly people and patients with disorders such as diabetes and Parkinson’s disease. Grading of the severity of OH and its effect on the patient’s quality of life are important. The symptoms vary with orthostatic stress, and subtle symptoms such as tiredness and cognitive impairment should be recognised. Standard drug treatment for OH is effective but worsens supine hypertension, whereas pyridostigmine can improve OH slightly but significantly without worsening of supine hypertension. Because orthostatic stress varies from moment to moment and drug treatment is suboptimal, drug treatment of OH needs to be combined with non-pharmacological approaches, such as compression of venous capacitance beds, use of physical counter-manoeuvres, and intermittent water-bolus treatment.

Introduction

Orthostatic hypotension (OH) or postural hypotension is common in elderly people and patients who have disorders that increase in incidence with age. Neurogenic OH can occur secondary to neuropathy (e.g., in diabetes or an autoimmune disease) or to a central lesion (e.g., in Parkinson’s disease or multiple system atrophy). This update will focus on three areas: recent advances in pharmacological management of OH, with emphasis on drugs clinically proven to be efficacious; coupling of pharmacological with non-pharmacological methods to improve orthostatic blood pressure, because OH varies with varying orthostatic stress; and patient-oriented management of OH.

A consensus definition of OH is a reduction of systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 3 min of standing up.1 The use of a tilt table in the head-up position at an angle of at least 60° is accepted as an alternative. OH can be symptomatic or asymptomatic; if the patient has symptoms that suggest OH inconclusively, measurements of blood pressure should be repeated or autonomic function should be tested. The screening values chosen to define OH are reasonable but are associated with a 5% false-positive rate; a 30 mm Hg fall in systolic blood pressure would reduce the frequency of false positives to 1%.2

With therapeutic advances, a quantitative approach to classification of orthostatic intolerance is important. A formal grading scale (panel 1)3 can be generated on the basis of the frequency and severity of symptoms, standing time before onset of symptoms, influence on activities of daily living, and blood pressure. A patient with grade I OH might not need drugs, whereas those with grades III or IV will need aggressive therapy. For monitoring of the course and severity of OH or the response to therapy, these individual components can be graded numerically with a self-report orthostatic grading score (panel 2).4 This validated scoring scheme was derived from the autonomic symptom profile5 and correlates well with severity and distribution of autonomic failure. It scores symptoms of orthostatic intolerance on the basis of frequency, severity, response to orthostatic stressors, interference with activities of daily living, and standing time,5 and generates a score from 0 (no symptoms) to 20 (maximum symptoms or dysfunction; panel 2). This scale is a practical way to monitor the status of OH and response to therapy. Although these scales are optional, documentation of the severity of symptoms, their relation to orthostatic stressors, and the influence of OH on activities of daily living and standing time are all important.

Panel 1: Symptom grade of orthostatic intolerance

| Grade I | Orthostatic symptoms are infrequent, inconstant, or only under conditions of increased orthostatic stress
| Standing time typically ≥15 min 
| Unrestricted activities of daily living 
| Blood pressure indices might or might not be abnormal |
| Grade II | Orthostatic symptoms develop at least once a week. Orthostatic symptoms commonly develop with orthostatic stress |
| Standing time ≥5 min on most occasions |
| Some limitation in activities of daily living |
| Some change in cardiovascular indices. These might be OH, reduction in pulse pressure ≥50%, or excessive oscillations in blood pressure |
| Grade III | Orthostatic symptoms develop on most occasions, and are regularly unmasked by orthostatic stressors |
| Standing time ≥1 min on most occasions |
| Marked limitation in activities of daily living |
| OH ≥50% of the time, recorded on different days |
| Grade IV | Orthostatic symptoms consistently present |
| Standing time <1 min on most occasions |
| Serious incapacitation; bed-bound or wheelchair-bound because of orthostatic intolerance. Syncope or presyncope is common if the patient attempts to stand |
| OH is consistently present |

From Low and colleagues.4
Review

Panel 2: Orthostatic symptom score
The patient is instructed to select appropriate answer.

Frequency of orthostatic symptoms
0  I never or rarely experience orthostatic symptoms when I stand up
1  I sometimes experience orthostatic symptoms when I stand up
2  I often experience orthostatic symptoms when I stand up
3  I usually experience orthostatic symptoms when I stand up
4  I always experience orthostatic symptoms when I stand up

Severity of orthostatic symptoms
0  I do not experience orthostatic symptoms when I stand up
1  I experience mild orthostatic symptoms when I stand up
2  I experience moderate orthostatic symptoms when I stand up and sometimes have to sit back down for relief
3  I experience severe orthostatic symptoms when I stand up and frequently have to sit back down for relief
4  I experience severe orthostatic symptoms when I stand up and regularly faint if I do not sit back down

Conditions under which orthostatic symptoms occur
0  I never or rarely experience orthostatic symptoms under any circumstances
1  I sometimes experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
2  I often experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
3  I usually experience orthostatic symptoms under certain conditions, such as prolonged standing, a meal, exertion (eg, walking), or when exposed to heat (eg, hot day, hot bath, hot shower)
4  I always experience orthostatic symptoms when I stand up; the specific conditions do not matter

Activities of daily living
0  My orthostatic symptoms do not interfere with activities of daily living (eg, work, chores, dressing, bathing)
1  My orthostatic symptoms mildly interfere with activities of daily living (eg, work, chores, dressing, bathing)
2  My orthostatic symptoms moderately interfere with activities of daily living (eg, work, chores, dressing, bathing)
3  My orthostatic symptoms severely interfere with activities of daily living (eg, work, chores, dressing, bathing)
4  My orthostatic symptoms severely interfere with activities of daily living (eg, work, chores, dressing, bathing). I am bed-bound or wheelchair-bound because of my symptoms

Standing time
0  On most occasions, I can stand as long as necessary without experiencing orthostatic symptoms
1  On most occasions, I can stand more than 15 min before experiencing orthostatic symptoms
2  On most occasions, I can stand 5–14 min before experiencing orthostatic symptoms
3  On most occasions, I can stand 1–4 min before experiencing orthostatic symptoms
4  On most occasions, I can stand less than 1 min before experiencing orthostatic symptoms

The prevalence of OH is high and related to aging. Most estimates of prevalence in cross-sectional groups of people 65 years of age or older are 5–30%, depending in part on the definition of OH, how the population is defined (eg, by age range or institution), the composition of the population (eg, healthy or select groups), the role of drugs, and the extent of orthostatic stress. The occurrence of OH is even higher in patients with autonomic disorders such as Parkinson’s disease, multiple system atrophy, and the autonomic neuropathies.

Clinical manifestations
OH is usually classed as asymptomatic, although most patients with asymptomatic OH have subtle symptoms in conditions of increased orthostatic stress, such as after a meal, during raised ambient temperature, or after exertion. Light-headedness is common, as expected, but many patients have more subtle symptoms, such as tiredness or difficulty in concentrating and thinking. In patients over 70 years of age, this impairment might be the most common symptom and, although subtle, it seriously impairs quality of life. Palpitations, tremulousness, anxiety, and nausea are symptoms of autonomic hyperactivity and occur in patients with OH who have only partial autonomic failure, typically seen in the autonomic neuropathies and in younger patients.

Symptoms are typically worse in the early morning, after meals, during a rise in core temperature, during prolonged standing, and with activity. The early morning severity of OH relates to nocturnal diuresis in many patients. Postprandial worsening of OH is common, occurring within 30 min and lasting for about 1 h. Paradoxically, such worsening might not occur in advanced autonomic failure, when the splanchnic-mesenteric bed can no longer vasodilate postprandially. Patients will commonly recognise that they have more symptoms after a hot bath, after time in a hot tub, or on a hot day. Indeed, any stress that results in vasodilatation of skin vessels will worsen symptoms. Patients who get up in the middle of the night out of a warm bed are vasodilated and have worse OH than if they get up from a colder environment; similarly, symptoms might be worse after ingestion of alcohol because of vasodilatation. With physical activity sufficient to cause muscle vasodilation, OH is also worse, owing to cerebral hypoperfusion. When OH is severe and sustained, syncope will occur. However, syncope is less common after diagnosis, because patients learn to recognise the symptoms of OH and take corrective steps.

Pathophysiology and pathogenesis
The maintenance of postural normotension without an excessive increase in heart rate depends on an adequate blood volume, and the integration of many reflex and humoral systems and several key vascular beds, including the striated muscle, splanchnic-mesenteric, and cerebrovascular beds.
Hypovolaemia will regularly cause OH, even if vascular reflexes are intact. Hypovolaemia can also be relative; for example, denervation decreases vascular tone and increases vascular capacity, and a patient with failure of norepinephrine-mediated signalling will be relatively hypovolaemic, although their plasma volume is normal. These patients can improve orthostatic intolerance if their plasma volume is expanded, hence the importance of volume expansion in the treatment of OH. Reduced erythrocyte mass or the normocytic, normochromic anaemia of chronic autonomic failure will also aggravate OH. Correction of anaemia with erythropoietin will improve orthostatic intolerance.

Two sets of baroreflexes, the arterial (or high-pressure) and venous (or low-pressure) baroreflexes, are mainly responsible for the reflex control of blood pressure and circulation (figure 1). When systemic pulse pressure or mean arterial pressure falls, arterial baroreceptors in the carotid sinus and aortic arch are unloaded. Afferent information from the carotid sinus travels via the glossopharyngeal nerve, and that from the carotid arch travels via the vagus nerve, to the nucleus of the tractus solitarius; from this structure, a polysynaptic cardiovagal pathway travels to the nucleus ambiguous and dorsal motor nucleus of the vagus nerve, and thence as the vagus to the sinoatrial node. Sympathetic function is regulated via the rostral ventrolateral medulla to the intermediolateral column of the thoracic cord to provide sympathetic innervation to the heart and peripheral arterioles and venules.

Low-pressure baroreceptors are activated by a reduction in central venous pressure (ie, they respond to changes in volume). Cardiopulmonary receptors in the heart and lungs send mainly non-myelinated vagal afferents to the nucleus of tractus solitarius; the central pathways and efferents are the same as for arterial baroreceptors. Baroreflex failure, especially if sympathetic efferents are affected, often results in the triad of OH, supine hypertension, and a loss of homeostatic ability to vary blood pressure; blood pressure is therefore higher at night than during the day.

The splanchnic-mesenteric capacitance bed is a large-volume, low-resistance system that constitutes 25–30% of total blood volume. There is much clinical and research evidence to support the importance of this bed and splanchnic outflow in the maintenance of postural normotension. Unlike muscle veins, the splanchnic veins have an abundance of smooth muscle and a rich sympathetic innervation, largely from the greater splanchnic nerve. This nerve has its cell body in the intermediolateral column (mainly T4–T9) and synapses at the coeliac ganglion, from where postganglionic adrenergic fibres supply effector cells. The mesenteric capacitance bed is responsive to both arterial and venous baroreflexes, and constriction of splanchnic veins is mediated by α-adrenoceptors.

OH occurs regularly after bilateral splanchic neurctectomy, but not after bilateral lumbar sympathectomy or cardiac denervation alone. In patients with complete spinal cord lesions, postural hypotension becomes most pronounced when the splanchic outflow is affected (when damage is above T6). Abnormalities in the splanchic autonomic outflow have been found in human diabetic neuropathy; both demyelination and loss of axons in this disorder suggest that preganglionic fibres are affected.

Cerebral vasoregulation is important to ensure adequate and stable blood flow to the brain despite variations in systemic blood pressure (autoregulation). Within a mean blood pressure range of about 50–150 mm Hg, a change in blood pressure results in an insignificant change in cerebral perfusion. Studies in patients with OH have shown an expansion of the autoregulated range at both the upper and lower limits, so that cerebral perfusion remains relatively constant when the patient is supine (when supine hypertension might occur) and in response to standing (when OH occurs), hence the common absence of symptoms.

**Management**
There are four interrelated goals in the treatment of OH: to improve orthostatic blood pressure without excessive supine hypertension; to improve standing time; to relieve orthostatic symptoms; and to improve the patient’s ability in orthostatic activities of daily living.

Symptoms of OH can always be relieved, but to do so without inducing unacceptable supine hypertension is
difficult, because patients with generalised autonomic failure have impaired baroreflexes and the loss of postural regulation of blood pressure is common. Patients with neurogenic OH have greater fluctuations in blood pressure than do people without OH (owing to the loss of baroreflexes or buffer nerves) and will commonly have supine hypertension. A practical goal is a regimen that relieves symptoms for most of the day with a supine blood pressure that does not usually exceed 180/110 mm Hg (this value is acceptable because patients are taught not to lie flat). Satisfactory control of blood pressure in OH without aggravation of supine hypertension has become easier with recent advances such as greater use of pyridostigmine.

Patients with asymptomatic OH do not require treatment. However, this statement needs to be qualified by the fact that most patients with OH will have symptoms at some time. The orthostatic stresses might be an early time of day, a meal, a rise in core temperature, physical activity, or reduced salt or fluid intake. Older patients might become symptomatic after a period of bed rest or after starting certain drugs. Common culprits are diuretics, antagonists of α-adrenoceptors to treat prostatism, antihypertensive drugs, and calcium channel blockers. Insulin, levodopa, or tricyclic antidepressants can also cause vasodilatation and OH in predisposed patients.

**Non-pharmacological management**

Pharmacological management alone is never adequate because orthostatic stress varies with circumstances, including time of day, meals, ambient temperature, and orthostatic stress. Education of patients is crucial. The patient should be told in simple terms about the maintenance of postural normotension and its practical implications (importance of blood volume, venous pooling, muscle contraction, and postural training). They need to be aware of orthostatic stressors and understand their mechanisms.

All patients with neurogenic OH need the standard treatment for OH, which aims to expand blood volume; vasoconstrictor drugs are ineffective when plasma volume is significantly reduced. Fluid intake of 1.25–2.50 L/day is crucial but is often neglected in elderly people. Salt supplementation is also essential. Most patients manage with salt added to meals but some prefer to use salt tablets (eg, 0.5 g or 1.0 g tablets). Many patients who have inadequate control of OH have an inadequate salt intake. This can be verified by checking the 24-h urinary sodium concentration: patients who have a value below 170 mmol can be treated with 1–2 g supplemental sodium three times a day, and their weight, symptoms, and urinary sodium concentrations checked 1 or 2 weeks later.46

The head of the patient’s bed should be elevated 10 cm to reduce nocturia and the effects of supine hypertension. During the day, adequate orthostatic stress should be maintained. In patients with OH who are repeatedly tilted up, OH is gradually attenuated; this might be because standing could cause extravasation of plasma around veins, providing a vascular cuff that increases venomotor tone.

In some patients, the use of a tightly fitting body stocking ameliorates OH and associated symptoms. The stockings work by reduction of the venous capacitance bed, although they have to be well fitted and put on before the patient arises, and the cumbersome application and discomfort in hot weather are disadvantages. A measured Jobst stocking is particularly useful but patients generally prefer an abdominal binder, which provides two-thirds of the benefits of a full Jobst stocking, combined with leg stockings.46

Water-bolus treatment is a useful orthostatic aid. The patient drinks in rapid succession two 250 mL glasses of water, which increases standing systolic blood pressure by more than 20 mm Hg for about 2 h.45,46 The mechanism involves activation of sympathetic adrenergic neurons; plasma concentrations of norepinephrine increase, and the effect can be abolished with trimetaphan.46

Physical counter-manoeuvres can help to prolong the time for which the patient can be upright. These manoeuvres include toe raising, leg crossing, thigh contraction, and bending at the waist (figure 2), which reduce venous capacity and increase total peripheral resistance.47,48 There is a training biofeedback effect, so the patient can improve the pressor effect by practising the manoeuvre with continuous recording of blood pressure.47,48

**Pharmacological management**

Drug treatment is an important part of overall therapeutic regimen and, if well used, will greatly enhance control of blood pressure.49 Midodrine, which has been approved for treatment of OH in some European countries, is the only drug approved by the US Food and Drug Administration to treat OH; other drugs are used off-label in the USA.

**Midodrine**

The only drug that has been shown in a double-blind, placebo-controlled study to improve OH and orthostatic symptoms is midodrine, a direct agonist of α1-adrenoceptors. The minimum effective dose is 5 mg but most patients respond best to 10 mg. Onset of action is 0.5–1.0 h after the drug is taken and the effect lasts for 2–4 h; these timings correspond to peak blood concentrations of the prodrug midodrine and its active metabolite desglymidodrine, respectively.49 Patients who have a duration of action of less than 4 h do best with an increased frequency of dosing (to every 3 h) during the period of maximum orthostatic stress, to avoid swings between severe hypotension and hypertension. The main side-effects are supine hypertension, paresthesias (including troublesome scalp-tingling), and goose-bumps. In a double-blind study,49 we showed that midodrine will dose-dependently improve orthostatic blood pressure but unfortunately has an even greater effect on supine blood
pressure. This effect is a major limitation to the use of midodrine because baroreflex failure is consistently associated with supine hypertension. Guidelines for the use of midodrine have become relatively standard: patients are advised to take the drug before getting out of bed, before lunch, and mid-afternoon. They are advised not to use the drug after 1800 h, to avoid nocturnal supine hypertension. They are also advised to omit a dose if supine or sitting blood pressure is 180/110 mm Hg or greater.

Pyridostigmine

In the search for a way to improve OH while supine hypertension is kept to a minimum, we sought a smart-drug approach. Baroreflex unloading occurs mainly with standing and is negligible when the patient is supine. Neurotransmission at autonomic ganglia is mediated by acetylcholine, which is rapidly hydrolysed by acetylcholinesterase. We argued that because pyridostigmine, a cholinesterase inhibitor, improves ganglionic transmission primarily when the patient is standing, this drug should increase ganglionic traffic proportional to the magnitude of orthostatic stress; hence, it should increase orthostatic blood pressure without worsening of supine blood pressure. We tested this hypothesis in an open study of 15 patients with neurogenic OH: 60 mg pyridostigmine improved OH, total peripheral resistance, and orthostatic symptoms without aggravation of supine hypertension.42 We followed this study with a double-blind randomised, four-way cross-over study of pyridostigmine in the treatment of 58 inpatients with neurogenic OH.43 The primary endpoint, on the basis of results from the open study, was improvement in diastolic blood pressure during standing. Pyridostigmine alone or combined with 5 mg midodrine significantly improved this endpoint without aggravation of supine blood pressure (figure 3), and the orthostatic symptoms improved proportionally to the improvement in standing blood pressure (figure 4).

What is the role of pyridostigmine in the management of OH? The main limitation of the drug is that it increases blood pressure only slightly (figure 3). For patients with mild OH, pyridostigmine alone is adequate. The dose is started at 30 mg two or three times a day and is gradually
increased to 60 mg three times a day. Its effectiveness can be enhanced, without occurrence of supine hypertension, by combining each dose of pyridostigmine with 5 mg midodrine. When full doses have been attained, some patients prefer to use the time-span form pyridostigmine (mestinon), which is a slow-release dose of 180 mg taken once each day. The main side-effects are related to dysfunction of the cholinergic system (eg, abdominal colic and loose motions).

**Other drugs**

Droxidopa (also known as L-threo-3,4-dihydroxyphenylserine or L-DOPS) is under study for the treatment of neurogenic OH and has been reported to improve OH. There is much interest in whether the drug improves OH with less supine hypertension than standard pressor drugs such as midodrine. Key to this discussion is the site of action of the drug: if its primary role is to replete postganglionic adrenergic axons, its release of norepinephrine should be proportional to ganglionic traffic and should result in less supine hypertension. It seems to improve OH even where there is a severe loss of postganglionic fibres (as in pure autonomic failure) and an extraneural source has been suggested; clinical pharmokinetic studies suggest both an extraneuronal and neuronal mode of action. Droxidopa seems to increase supine blood pressure variably—eg, in a small, double-blind, placebo-controlled study of ten patients with OH, the drug increased supine and standing blood pressure and activity of the noradrenergic system. Droxidopa is sometimes effective when other drugs have failed, and it is dramatically effective in the treatment of OH that is caused by deficiency of dopamine-β-hydroxylase.

**Fludrocortisone** expands plasma volume and increases sensitivity of α-adrenoceptors. It is usually used at a dose of 0·1–0·2 mg/day but occasionally is used at 0·4–0·6 mg/day. Supine hypertension and hypokalaemia are very common, especially at higher doses.

A pressor effect has been described for other drugs, including yohimbine, indomethacin, somatostatin, and dihydroergotamine, but their value in treatment of OH is controversial.

### Synthesis and conclusions

The management of neurogenic OH can be synthesised as follows. The presence of OH, its manifestations, its influence on activities of daily living, and its relationship to orthostatic stresses should be established. All patients need expansion of blood volume with increased intake of fluids and salt, supplemented in some cases with low-dose fludrocortisones. The patient should receive education on management of OH, the need to sleep with the head of the bed elevated, the use of physical counter-manoeuvres, compression garments, and the judicious use of water boluses. If drugs are needed, the combination of pyridostigmine and midodrine can be titrated. A major responsibility of management also shifts to the patient: the patient should provide a set of recordings, taken over a couple of days, of blood pressure sitting and standing up on awakening, before lunch, 1 h after lunch, and before retiring. If the patient has an automated blood-pressure unit, they should stand for 1 min and then activate the recording.

### Search strategy and selection criteria

References for this focused review were identified by searches of PubMed between 1995 and January, 2008, with the search term “orthostatic hypotension”. Articles were also identified through searches of the authors’ own files. Only papers published in English were selected. The final reference list was generated on the basis of originality and relevance to the topic covered in this review, with a particular focus on data supported by clinical trials.
References

Confl icts of interest
We have no conﬂicts of interest.

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