Orthostatic hypotension is the most incapacitating symptom of autonomic failure. Fortunately, with the help of non-pharmacological and pharmacological interventions, most patients’ quality of life can be improved substantially. The therapeutic interventions to treat patients with orthostatic hypotension should be implemented in stages and depend, in large part, on the severity of symptoms. Some patients may be markedly improved by education, counseling, removal of hypotensive medications and other non-pharmacological interventions, while more severely afflicted patients require pharmacological interventions [9].

Non-pharmacological measures

Patient education is the cornerstone of the management of orthostatic hypotension. Throughout the day, patients are subject to a number of orthostatic demands for which there are simple but effective countermeasures. The time spent with patients emphasizing these practical management principles is of inestimable value. These include moving from a supine to standing position in gradual stages; avoiding orthostatic stress in the morning when orthostatic tolerance is lowest [24]; minimizing straining and isometric exercise; should be discouraged; and avoiding deconditioning. Frequent small meals are preferable as food ingestion often exacerbates orthostatic hypotension [19, 32]. Physical counter-maneuvers such as leg-crossing and squatting may be used to facilitate cerebral perfusion by increasing central blood volume and cardiac filling pressures [39]. The use of custom fitted elastic stockings may also be used to provide a graded pressure to the lower extremity and abdomen. Medications such as diuretics, anti-hypertensive agents, anti-anginal agents, anti-depressants and alpha adrenoceptor antagonists should be tapered as these can cause or exacerbate orthostatic hypotension.

Abstract

Orthostatic hypotension is treated effectively with the combined use of non-pharmacological and pharmacological interventions. Patients should be counseled as to the nature of the underlying disorder and reversible causes of orthostatic hypotension should be removed. Should symptoms persist, pharmacological treatment is implemented. First line pharmacotherapeutic interventions include volume repletion in combination with alpha-adrenoceptor agonists. If unsuccessful there are several supplementary agents with different mechanisms of action that may provide an additive effect.

Key words

orthostatic hypotension · syncope · autonomic failure · sympathetic nervous system
Volume expansion

Administration of fluid and sodium chloride

Plasma volume expansion is essential to improve orthostatic tolerance. The high nocturnal blood pressure causes a pressure natriuresis and results in nocturnal volume and sodium chloride depletion. Several measures are available for maintaining and repleting plasma volume (See Table 1). Patients should have a daily dietary intake of least 10 g (185 mmol) of sodium per day accompanied by an increase in fluid intake of 2–2.5 l (in adults) per day. An early morning body weight gain of about 1–2 kg usually implies adequate extra-cellular fluid volume expansion [38].

Ingestion of approximately 500 cc of tap water elicits a marked pressor response and improvement in symptoms in patients with autonomic failure. The pressor response, a systolic blood pressure increase of over 30 mmHg in some patients, is evident within 5 minutes after the water ingestion [14].

9-α-Fluorohydrocortisone

9-α-Fluorohydrocortisone (fludrocortisone acetate), a synthetic mineralocorticoid, may be used if patient are unable to increase plasma volume effectively with fluid and salt [3, 11, 18]. This agent has a long duration of action and is well-tolerated by most patients. Fludrocortisone increases the blood volume and enhances the sensitivity of blood vessels to circulating catecholamines [7, 11]. Other potential modes of action include enhancing norepinephrine release from sympathetic neurons and increasing vascular fluid content [34].

Treatment is initiated with a 0.1 mg tablet and can be increased to 0.3–0.5 mg daily [38]. Treatment may unfortunately be limited by supine hypertension due to an increase in the peripheral vascular resistance [4]. Other side effects include ankle edema, hypokalemia, headache and rarely congestive heart failure. Potassium supplementation is usually required, particularly when higher doses are used.

Vasopressin analogs

The vasopressin analogs may be used to supplement volume expansion. Arginine-vasopressin has a circadian rhythm that peaks during the night. Thus, the increase in nocturnal urinary excretion in patients with autonomic failure, which is in part due to the increase in supine blood pressures, is also due to loss of vasopressin neurons in the suprachiasmatic nucleus of the hypothalamus and the ensuing loss of the normal AVP circadian rhythm [27].

The potent, synthetic vasopressin analog desmopressin acetate (DDAVP) acts on the V2 receptors in the collecting ducts of the renal tubules and prevents nocturia, weight loss and reduces the morning postural fall in blood pressure. DDAVP is usually administered as a nasal spray (5–40 μg) or orally (100–800 μg). Adverse events include water intoxication and hyponatremia [21]. Low doses of intranasal desmopressin (5 μg) may be sufficient to attenuate the nocturnal diuresis without placing the patient at risk for hyponatremia [33].

Sympathomimetic agents

The administration of sympathomimetic agents is central to the management of patients with cardiovascular autonomic failure. Thus, if symptoms of orthostatic intolerance persist once intravascular volume is replenished the direct or indirect adrenergic agonists and antagonists should be administered (See Table 2). The pressor response of these agents is due to the reduction in venous capacity and the constriction of the resistance vessels.

The available α1-adrenoreceptor agonists include those with direct and indirect effects (ephedrine, pseudoephedrine), those with direct effects (midodrine and phynylephrine) and those with only indirect effects (methylphenidate and dextroamphetamine sulphate).

The peripheral selective direct, α1-adrenoreceptor agonist midodrine is the only agent approved by the FDA for the treatment of orthostatic hypotension [20]. Its efficacy has been demonstrated in double-blind placebo controlled studies [15, 20, 42]. Mido drine, the prodrug is activated to desglymidodrine, the active α-adrenoreceptor agonist. Midodrine has an elimination half life of 0.5 hours and is undetectable in plasma 2 hours after an oral dose. The agent undergoes enzymatic hydrolysis (deglycination) in the systemic circulation to form the active agent, desglymidodrine. Desglymidodrine is 15 times more potent than midodrine and is primarily responsible for the therapeutic effect. The elimination half-life of

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Volume expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid and sodium chloride</td>
<td>9-α-Fluorohydrocortisone</td>
</tr>
<tr>
<td>Vasopressin analogs</td>
<td>Acute water ingestion</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Sympathomimetic agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midodrine</td>
<td>Ephedrine</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>15</td>
</tr>
</tbody>
</table>
Desglymidodrine is 2–4 hours. Desglymidodrine is predominantly excreted by the kidneys.

Patient sensitivity to this agent varies and the dose should be titrated from 2.5 mg to 10 mg three times a day. The peak effect of this agent occurs 1 hour after ingestion [42]. Potential side effects of midodrine include pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention. Central nervous system side-effects occur infrequently.

The mixed α-adrenoreceptor agonists—which act directly on the α-adrenoreceptor and release norepinephrine from the post-ganglionic sympathetic neuron—include ephedrine, pseudoephedrine. There are structural, pharmacological and therapeutic differences between these agents and midodrine. Ephedrine is an agonist of α, β1 and β2 receptors. The β2 vasodilatory effects may attenuate the pressor effect of this drug. Pseudoephedrine, a stereoisomer of ephedrine has similar pharmacological and therapeutic properties [13]. Typical doses of the agents are ephedrine: 25–50 mg three times a day; and pseudoephedrine: 30–60 mg three times a day. Because the effectiveness of these agents is at least in part due to the release of norepinephrine from the post-ganglionic neuron, these medications are in theory most likely to benefit patients with partial or incomplete lesions [1, 6, 10]. The indirect agonists, methylphenidate and dextroamphetamine, that release norepinephrine from post-ganglionic neurons are infrequently used to treat orthostatic hypotension. In a small head-to-head trial midodrine (mean dose 8.4 mg tid) improved standing blood pressure and orthostatic tolerance more than ephedrine (22.3 mg tid) [8]. In another trial, phenylpropanolamine (12.5 mg) and yohimbine (5.4 mg) produced equivalent increases in standing systolic blood pressure while methylphenidate failed to increase standing systolic blood pressure significantly [13].

The use of the sympathomimetic agents (with the possible exception of midodrine) may be complicated by tachyphylaxis, although efficacy may be regained after a short drug holiday. The central sympathomimetic side-effects such anxiety, tremulousness and tachycardia that invariably accompany the use of these agents are frequently intolerable to patients. Midodrine, which does not cross the blood brain barrier in significant amounts, does not have these central sympathomimetic side-effects. There is evidence that phenylpropanolamine increases the risk of hemorrhagic stroke in women [16] and the FDA has suggested that phenylpropanolamine be removed from all drug products.

Severe hypertension is an important adverse-effect of all sympathomimetic agents. Patients should not take these medications for 4 hours prior to recumbency. Patients taking midodrine report piloerection, pruritus and tingling. These are most likely peripheral sympathomimetic effects of the drug.

### Supplementary therapy

There are rare patients who do not respond to first line interventions and require additional agents to treat their symptoms. These supplementary agents may provide an additive therapeutic effect to the first-line therapies (see Table 3).

#### Acetylcholinesterase inhibition

The acetylcholinesterase inhibitor, pyridostigmine, (60 mg) administered orally increased head-up tilt blood pressure and reduced orthostatic hypotension in patients with neurogenic orthostatic hypotension. The associated increase in supine blood pressure may not be as great as that seen with other pressors. Twenty percent of patients report cholinergic side-effects. The rationale for the use of this agent is that inhibition of acetylcholinesterase enhance sympathetic ganglionic neurotransmission and that the effect is maximal while upright, when sympathetic nerve traffic is greatest [35].

#### Caffeine

The methylxanthine caffeine has a well-established, although modest, pressor effect that is in part due to blockade of vasodilating adenosine receptors. The pressor effect is subject to tachyphylaxis. Typical caffeine doses are 100–250 mg three times a day, either as tablets or caffeinated beverages (one cup of coffee contains approximately 85 mg of caffeine and one cup tea contains 50 mg of caffeine) [25].

#### Erythropoietin

Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension [12, 28]. This agent corrects the normochromic normocytic anemia that frequently accompanies autonomic failure [2, 41] and diabetic autonomic neuropathy [40].

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Supplementary therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholinesterase inhibition</td>
<td>Caffeine</td>
</tr>
</tbody>
</table>

## Glosary

- **Desglymidodrine:** A drug used to treat orthostatic hypotension.
- **Ephedrine:** An α, β1, and β2 agonist used to treat hypotension.
- **Pseudoephedrine:** A stereoisomer of ephedrine.
- **Midodrine:** A mixed α-adrenoreceptor agonist used to treat orthostatic hypotension.
- **Orthostatic hypotension:** A condition where blood pressure drops significantly when standing up.
- **Sympathomimetic agents:** Drugs that stimulate the sympathetic nervous system.
- **Acetylcholinesterase inhibition:** Inhibiting the enzyme that breaks down acetylcholine, leading to increased blood pressure.
- **Caffeine:** A methylxanthine that increases blood pressure.
- **Erythropoietin:** A hormone that increases blood pressure and improves orthostatic tolerance.
Recombinant human erythropoietin, erythropoietin alpha, is administered subcutaneously or intravenously at doses between 25 and 75 U per kg three times a week until a hematocrit that approaches normal is attained. Lower maintenance doses (approximately 25 U per kg three times a week) may then be used. Iron supplementation is usually required, particularly during the period when the hematocrit is increasing. Erythropoietin increases red cell mass and central blood volume although the precise mechanism of action of this agent is not resolved. There is evidence that the effect of erythropoietin is related to vascular tone regulation mediated by the interaction between hemoglobin and the vasodilator nitric oxide [29]. Supine hypertension may accompany the use of erythropoietin [12, 28].

**β-Blockers**

Nonselective β-blockers, particularly those with intrinsic sympathomimetic activity such as pindolol and xamoterol, may have a limited place in the treatment of orthostatic hypotension despite the well-acknowledged negative chronotropy and inotropy associated with these medications [5, 22, 23, 37]. The suggested mechanism of action of these medications is the blockade of vasodilating β-2 receptors allowing unopposed α-adrenoreceptor mediated vasoconstrictor effects to dominate. The pressor effect of these agents has not been demonstrated consistently in clinical trials [17].

**Clonidine**

Clonidine is an α2 agonist that usually produces a central, sympatholytic effect and a consequent decrease in blood pressure. In patients with autonomic failure, who have little central sympathetic efferent activity, the effect of this agent on post synaptic α2 adrenoreceptors may predominate. The use of clonidine (0.1–0.6 mg per day) could therefore result in an increase in venous return without a significant increase in peripheral vascular resistance although mechanism of action is still not clearly defined [36]. The use of this agent, at least theoretically, is limited to patients with severe central autonomic dysfunction in whom there is no ostensible effect of further sympatholysis and the peripheral effect may dominate [30, 31]. Clonidine should be used cautiously as exacerbation of hypotension may occur. Side-effects include somnolence, xerostomia and constipation.

**Yohimbine**

Yohimbine is a centrally and peripherally active selective α2 adrenoreceptor antagonist that increases sympathetic nervous system efferent output by antagonizing central or presynaptic α2-adrenoreceptors or both. This agent, theoretically, should be more effective in patients that have some residual sympathetic nervous system output, although this has not always been borne out in clinical studies. Side effects of yohimbine include anxiety, tremor, palpitations, diarrhea and supine hypertension [13, 26].

**Conclusion**

With the help of non-pharmacological and pharmacological interventions, most patients' quality of life can be improved substantially. Treatment should be initiated in stages. First, patients should be counseled as to the nature of the underlying disorder and reversible causes of orthostatic hypotension should be removed. If symptoms persist, pharmacological treatment is implemented. Many patients will be adequately treated by education, counseling, removal of hypotensive medications and other non-pharmacological interventions while more severely afflicted patients require pharmacological interventions.

**Disclosure** Dr. Freeman has served as a consultant for Chelsea Therapeutics.

**References**
