

TREATMENT OF AUTONOMIC NEUROPATHY

TREATMENT OF ORTHOSTATIC HYPOTENSION (Part One)

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Introduction

Man's evolution from a quadrupedal to a bipedal animal, with the accompanying move from a horizontal to an erect posture, placed considerable demands on the ability of the cardiovascular system to maintain adequate cerebral blood flow.^{1, 3} The assumption of the upright posture results in a complex sequence of physiological reactions in response to the pooling of 500 to 1000 ccs of blood in the lower extremities and splanchnic circulation. There is a decrease in venous return to the heart and the reduced ventricular filling results in diminished cardiac output and blood pressure. These hemodynamic changes provoke a baroreceptor initiated compensatory reflex mediated via the central nervous system and effected by the peripheral efferent autonomic outflow.

The lower arterial pressure results in a reduction in the frequency of afferent impulses relayed from the arterial baroreceptors and (to a lesser extent) cardiopulmonary volume receptors to the nucleus of the tractus solitarius (NTS) in the dorsomedial medulla via cranial nerves IX and X. The reduction in baroreceptor mediated tonic inhibition produces a decrease in vagal nerve activity (mediated by the neuroanatomical connections of the NTS to the nucleus ambiguus) and an increase in sympathetic efferent activity (mediated by the NTS connections to the rostral ventrolateral medulla and intermediolateral column).³⁻⁵

This baroreceptor reflex activity results in constriction of the capacitance and resistance vessels and an increase in heart rate and myocardial contractility. These compensatory mechanisms increase the peripheral resistance, venous return, and cardiac output, and thus limit the fall in blood pressure. The normal response to the assumption of the erect posture is a fall in systolic blood pressure (5–10 mm Hg), an increase in diastolic blood pressure (5–10 mm Hg) and an increase in the pulse rate (10–25 beats per minute).^{6, 7} Should these mechanisms fail, the symptoms of cerebral hypoperfusion will ensue.

Orthostatic hypotension is the most incapacitating symptom of autonomic failure. Severely afflicted patients are unable to leave the supine position without experiencing symptoms of presyncope or losing consciousness. Orthostatic hypotension is not necessarily the first symptom of the disorder, although it is the symptom that usually leads patients to seek medical attention. Patients typically present with lightheadedness and presyncopal complaints that occur in response to sudden postural change, meals, exertion, or prolonged standing. Complaints less easily recognized as hypotensive in origin, such as generalized weakness, fatigue, cognitive slowing, leg buckling, visual blurring, headache, and neck pain also may be present. The visual complaints most likely represent retinal or occipital lobe ischemia. Neck pain, which may be the only symptom of orthostatic hypotension, is most likely a consequence

of neck muscle ischemia. Loss of consciousness may be of gradual onset or can occur suddenly, raising the possibility of a seizure or cardiac cause. Some patients may display coarse jerking movements and, rarely, focal neurological findings. The appearance of focal findings may suggest underlying cerebrovascular disease.⁸ Patients with autonomic failure accommodate to their orthostatic hypotension and frequently are able to tolerate significant falls in blood pressure (even to the 40–50 mm Hg level) without symptoms. This may in part be due to a shift to the left of the lower limit of cerebral autoregulation, the capacity to maintain constant cerebral blood flow despite changes in the perfusion pressure. Thomas and Bannister⁹ showed that cerebral blood flow was normally maintained in patients with autonomic failure until the mean arterial pressure fell to 40 mm Hg in comparison to 60–70 mm Hg in normal subjects.

Orthostatic hypotension occurs as a consequence of primary degeneration of the central or peripheral ANS. Multiple system atrophy (MSA), the Shy–Drager syndrome, is a central autonomic degenerative disorder in which the autonomic dysfunction is accompanied by degeneration of other neuronal groups in the extrapyramidal, pyramidal and cerebellar systems.^{10–13} Orthostatic hypotension may also accompany Parkinson's disease and other central nervous system disorders.^{14,15} Pure autonomic failure (PAF) results in progressive autonomic failure characteristically without other associated signs or symptoms of peripheral neuropathy or central nervous system disease.^{11,16–18} Peripheral autonomic dysfunction may also accompany small fiber peripheral neuropathies such as those seen in diabetes, amyloid, hereditary sensory and autonomic neuropathies (HSAN III and IV) and inflammatory neuropathies. Less frequently, orthostatic hypotension is associated with the peripheral neuropathies accompanying porphyria, vitamin B₁₂ deficiency, and HIV infection.^{19, 20}

The hallmark of both central and peripheral causes of neurogenic orthostatic hypotension is the failure to release norepinephrine appropriately upon standing. Normally, norepinephrine is released into the synaptic cleft in response to standing, resulting in a 2–3 fold increase in plasma norepinephrine.^{21, 22} Patients with neurogenic orthostatic hypotension due to PAF or a small fiber peripheral neuropathy typically have low resting norepinephrine levels, due to degeneration of the post–ganglionic neuron. Patients with MSA (in which the post–ganglionic neuron remains intact) have normal supine norepinephrine levels. Neither patient group demonstrates an increase in plasma norepinephrine upon standing.^{21, 22} However, considerable overlap exists between these two patient groups, which limits the ability to make a definitive diagnosis based on plasma catecholamine measurements in individual patients.^{23–25}

Treatment

Therapeutic measures for neurogenic orthostatic hypotension are numerous, diverse, yet remain deficient. The sheer number of therapeutic modalities pharmacological agents underscores the inadequacy of the available treatment.

a. 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.

Patients with orthostatic hypotension should move from a supine to standing position in gradual stages particularly in the morning, when orthostatic tolerance is lowest. Maneuvers such as straining, coughing, and raising the arms above the head should be avoided. These maneuvers

may reduce venous return and induce symptoms of hypotension. Similarly, isometric exercise should be discouraged. Prolonged recumbency can markedly reduce orthostatic tolerance and physical activity and exercise should be strongly advocated. Isotonic exercise is recommended to avoid the reduction in venous return that is associated with straining. The hydrostatic pressure that accompanies swimming increases orthostatic tolerance during this activity. The hemodynamic consequences of exercise, warm weather, fevers, hot baths, and showers may present challenges to orthostatic tolerance. This is of particular importance in patients who lack appropriate thermo-regulatory sweating. Patients should be made aware of a number of physical maneuvers that can help maintain blood pressure during daily activities such as leg crossing, stooping, and squatting.²⁶

The recognition and removal of potential reversible causes of orthostatic hypotension is the first and most important management step. Medications such as diuretics, anti-hypertensive agents, anti-anginal agents, and anti-depressants are the most common offending agents. Paradoxically, the use of anti-hypertensive agents occurs frequently in patients with orthostatic hypotension, because of the coexistence of supine hypertension. Many patients will present with orthostatic hypotension shortly after treatment for supine hypertension is initiated. Orthostatic hypotension also commonly first manifests when a tricyclic antidepressant is introduced as therapy for a painful neuropathy. Nortriptyline and desipramine are tricyclic agents with a relatively low incidence of postural hypotension and their use may minimize this problem.²⁷ In contrast, patients with autonomic failure are sensitive to the hypertensive effects of over the counter medications such as sympathomimetic containing diet pills and cold remedies.²⁸ Even topical ophthalmic solutions may produce similar unwanted effects.²⁹

The excessive natriuresis and reduction in central blood volume can be attenuated or minimized by increasing sodium intake with high-sodium containing foods or salt tablets.⁷

Raising the head of the bed 10 to 20 degrees activates the renin-angiotensin-aldosterone system³⁰ and decreases the nocturnal diuresis. Raising the head of the bed may also reduce the supine hypertension that is prevalent in these patients, either as a consequence of baroreceptor denervation or as a side effect of treatment. Severe supine hypertension often limits therapeutic intervention, although surprisingly, most patients tolerate sustained supine blood pressures without untoward effect. The use of short acting antihypertensive agents at night or ingestion of small amounts of alcohol before retiring may be of benefit. Orthostatic tolerance, should the patient need to leave the supine position, may be severely impaired by these endeavors.

The use of custom fitted elastic stockings permit the application of a graded pressure to the lower extremity and abdomen. These stockings minimize peripheral blood pooling in the lower extremities and splanchnic circulation. It is essential that such stockings extend to the waist as most peripheral pooling occurs in the splanchnic circulation. These stockings are poorly tolerated by many patients, particularly those with painful peripheral neuropathies or motor dysfunction.

Patients with autonomic failure and even normal elderly are susceptible to significant falls in blood pressure associated with meals.^{31, 32} Post prandial hypotension can be minimized by avoiding large meals, ingesting meals low in carbohydrate, and minimizing alcohol intake. Patients should be advised against activities or sudden standing immediately after eating.

b. Pharmacological measures

The non-pharmacological measures unfortunately help only the mildly afflicted and pharmacological intervention is usually required. Numerous agents from diverse pharmacological groups have been implemented in the treatment of orthostatic hypotension (See Table I). The therapeutic goal is merely to ameliorate all symptoms while avoiding side effects. There is rarely the need to restore normotension.³³

i. Primary therapy

9- α -fluorohydrocortisone

9- α -fluorohydrocortisone (fludrocortisone acetate), a synthetic mineralocorticoid, is the medication of first choice for most patients with orthostatic hypotension.^{34, 35} 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.^{35, 36} Other potential modes of action include enhancing norepinephrine release from sympathetic neurons and increasing vascular fluid content.³⁷ Chobanian has suggested that sodium retention and plasma volume return to normal with long term use although the pressor effect persists due to increased peripheral vascular resistance.³⁸

Treatment is initiated with a 0.1 mg tablet and can be increased to 1 mg daily although little benefit is obtained by increasing beyond 0.5 mg. Treatment may unfortunately be limited by supine hypertension due to an increase in the peripheral vascular resistance.³⁸ Other side effects include ankle edema, hypokalemia, and rarely congestive heart failure. Potassium supplementation is usually required, particularly when higher doses are used.

Sympathomimetic Agents

A direct or indirect sympathomimetic agent can be added to fludrocortisone acetate should the patient remain symptomatic. These medications may also be used alone in patients unable to tolerate the side effects of fludrocortisone acetate. The effectiveness of the sympathomimetic agents is most likely dependent on the increase in receptor number and affinity and the reduction in baroreceptor modulation that accompanies autonomic failure. The available alpha-1 adrenoreceptor agonists include those with direct and indirect effects (ephedrine, pseudoephedrine, and phenylpropanolamine), those with direct effects (midodrine and phenylephrine) and those with only indirect effects (methylphenidate and dextroamphetamine sulphate). Ephedrine (25–50 mg t.i.d), pseudoephedrine (30–60 mg t.i.d) and phenylpropanolamine (12.5–25 mg t.i.d) are the most frequently prescribed agents. Because the effectiveness of the indirect agonists 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.^{28, 39–42}

The peripheral selective α -agonist midodrine is the only agent approved by the FDA for the treatment of orthostatic hypotension.⁴³ The pressor effect of midodrine is due to both arterial and venous constriction. The efficacy of this agent has been demonstrated in open-label and double-blind studies.^{43–45} Midodrine, the prodrug is activated to desglymidodrine the active α -adrenoreceptor agonist. Absorption as the prodrug may theoretically minimize direct vasoconstriction of the gastrointestinal tract. Midodrine is rapidly absorbed from the gastrointestinal tract. The peak plasma concentration of midodrine occurs in 20–40 minutes and the half-life is 30 minutes. The half-life of

desglymidodrine is 4 hours. Patient sensitivity to this agent varies and the dose should be titrated from 2.5 mg to 10 mg t.i.d. The peak effect of this agent occurs 1 hour after ingestion. Potential side effects of this agent include pilomotor reactions, pruritus, supine hypertension, gastrointestinal complaints, and urinary retention. Central nervous system side effects occur infrequently.

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 sympathomimetic side effects such as 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, does not have the central sympathomimetic side effects. Phenylpropanolamine may result in less central nervous system stimulation than the other agents. Severe supine hypertension, which occurs both as a consequence of baroreceptor denervation and as a side effect of treatment, often limits therapeutic intervention, although surprisingly, most patients tolerate sustained supine blood pressures without untoward effect.⁴⁶ Raising the head of the bed 10 to 20 degrees reduces supine hypertension and activates the renin–angiotensin–aldosterone system which decreases the nocturnal diuresis that is associated with autonomic failure. The use of short acting antihypertensive agents at night (such as topical nitrates, captopril, or nifedipine) or ingestion of small amounts of alcohol before retiring may be of benefit. Orthostatic tolerance may be severely impaired by these endeavors should the patient need to leave the supine position.

There were initial optimistic reports on the use of the indirect acting agent tyramine, which releases norepinephrine from neuronal storage pools, in combination with a monoamine oxidase inhibitor to prevent breakdown of the released norepinephrine. The use of this combination of pharmacological agents is unfortunately limited by severe supine hypertension, an unpredictable response and, in some cases, the failure to abolish orthostatic symptoms.

ii. Supplementary therapy

Cyclooxygenase inhibitors

The cyclooxygenase inhibitors such as indomethacin, flurbiprofen, and other non-steroidal anti-inflammatory agents may also reduce orthostatic hypotension. These medications are rarely effective as monotherapy, but may be used to supplement treatment with 9- α -fluorohydrocortisone or a sympathomimetic agent. The probable mode of action of the prostaglandin synthesis inhibitors is to limit the vasodilating effects of circulating prostaglandins and arachidonic acid derivatives. These agents may also increase the central circulating blood volume and enhance vascular sensitivity to circulating pressor amines.⁴⁷

Caffeine

The methylxanthine caffeine has a well-established pressor effect that is in part due to blockade of vasodilating adenosine receptors. Caffeine improves orthostatic hypotension and attenuates post-prandial hypotension in patients with autonomic failure. Typical caffeine doses are 100–250 mg t.i.d, 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).⁴⁸

Erythropoietin

Erythropoietin increases standing blood pressure and improves orthostatic tolerance in patients with orthostatic hypotension. This agent corrects the normochromic normocytic anemia that frequently accompanies autonomic failure.⁴⁹ Recombinant human erythropoietin, epoetin alpha, is administered subcutaneously or intravenously at doses between 25–75U per kilogram three times a week until a hematocrit that approaches normal is attained. Lower maintenance doses (approximately 25U per kilogram three times a week) may then be used. Iron supplementation is usually required, particularly during the period when the hematocrit is increasing. The mechanism of action for the pressor effect of this agent is unresolved. Possibilities include the increase in red cell mass and central blood volume, alterations in blood viscosity, and direct or indirect neurohumoral effects on the vascular wall. Supine hypertension may accompany the use of this agent.^{50,51} This agent is not effective in the treatment of orthostatic tachycardia.⁵²

iii. Tertiary and experimental agents

Somatostatin

Somatostatin and somatostatin analogues such as octreotide, the long acting synthetic octapeptide, attenuate the pancreatic and gastrointestinal hormone response to food ingestion and other stimuli. These agents attenuate the post-prandial blood pressure fall and reduce orthostatic hypotension in patients with autonomic failure. Mechanisms of action for these medications include a local effect on splanchnic vasculature by inhibiting the release of vasoactive gastrointestinal peptides, enhanced cardiac output, and an increase in forearm and splanchnic vascular resistance. Subcutaneous doses of octreotide range from 25 to 200 µg. Side effects of nausea and abdominal cramps limit the use of these agents.^{53, 54}

Dihydroxyphenylserine

Dihydroxyphenylserine (DOPS) is a synthetic, non-physiological, amino acid norepinephrine precursor that is decarboxylated by the ubiquitous L-amino acid decarboxylase to L-norepinephrine in both animals and man. The important role played by norepinephrine in the maintenance of upright blood pressure and the successful implementation of precursor therapy for Parkinson's disease provide the rationale for the use of this agent to treat neurogenic orthostatic hypotension. Of the four stereoisomers D- and L-threo-DOPS and D- and L-erythro-DOPS, only L-threo-DOPS is pharmacologically and biologically active. Patients with dopamine β-hydroxylase deficiency are unable to synthesize norepinephrine and epinephrine in the central and peripheral nervous system. Because the conversion of DOPS to norepinephrine bypasses the β-hydroxylation step, DOPS is the ideal therapeutic agent for this inherited disorder. This agent may also be of benefit in patients with familial amyloid polyneuropathy, Parkinson's disease, MSA and PAF.⁵⁵⁻⁵⁷

Dihydroergotamine

Dihydroergotamine, an ergot alkaloid that interacts with α-adrenergic receptors, has a selective venoconstrictor effect.^{58, 59} This medication may increase venous return in patients with orthostatic hypotension without producing a significant increase in the peripheral vascular resistance. Although dihydroergotamine is an effective pressor intravenously and intramuscularly, low oral bioavailability results in an inconsistent effect when taken orally.⁶⁰

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 inotropic associated with these medications. 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. Congestive heart failure may be a serious side effect of this medication.^{61, 62}

Vasopressin analogues

The vasopressin analogues have a limited place in the treatment of orthostatic hypotension. The postural release of arginine-vasopressin is reduced in patients with autonomic failure and patients with autonomic failure are supersensitive to exogenous vasopressin and vasopressin analogues. The synthetic vasopressin analogue desmopressin acetate (DDAVP) acts on the V2 receptors in the collecting ducts of the renal tubules and has no V1 receptor vasoconstricting potential. DDAVP, which can be taken as a nasal spray (10–40 mcg) or orally (100 – 800 mcg), prevents nocturia, weight loss, and reduces the morning postural fall in blood pressure in patients with autonomic failure. Fluid and electrolyte status should be carefully monitored during therapy avoid to hyponatremia.⁶³ The vasopressor analogues of vasopressin (V1 receptor agonists), such as lysine-vasopressin nasal spray and intramuscular triglycl-lysine vasopressin, may also increase blood pressure and peripheral vascular resistance and improve symptoms of orthostatic hypotension.⁶⁴

Clonidine

Clonidine is a α-2 antagonist 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 postsynaptic α-2 adrenoreceptors may predominate. These receptors may be more numerous on veins than arterioles. 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. 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. The hypertensive effect is inconsistent and in some patients residual sympathetic activity could be inhibited. The agent may cause profound hypotension in patients with autonomic failure.⁶⁵

Yohimbine

Yohimbine is a centrally active selective α-2 antagonist that increases sympathetic nervous system efferent output by antagonizing central or presynaptic α-2 receptors or both. Yohimbine (8 mg t.i.d) produces a modest pressor effect although theoretically patients should have some residual sympathetic nervous system output. Side effects of yohimbine include anxiety, tremor, palpitations, diarrhea, and supine hypertension.⁶⁶

Dopamine Antagonists

The dopamine antagonists metoclopramide and domperidone may also treat orthostatic hypotension. These agents most likely inhibit the vasodilating and natriuretic effect of dopamine or increase noradrenalin release due to blockade of prejunctional inhibitory

dopaminergic receptors. The risk of tardive dyskinesia and other extrapyramidal side effects limits the long-term use of these agents.⁶⁷

Conclusion

Orthostatic hypotension is the most incapacitating symptom of autonomic failure. Most patients can be treated successfully with a combination of fludrocortisone and a sympathomimetic agent. Caffeine, prostaglandin synthetase inhibitors, and erythropoietin are useful supplementary agents in patients with more refractory symptoms. Finally, there are rare patients who will require the addition of the tertiary and experimental agents to treat their symptoms. There is, however, a small group of patients who remain refractory to all therapeutic endeavors.

TABLE 1
Pharmacotherapy of orthostatic hypotension

Mineralocorticoids

9 α -fludrocortisone

Sympathomimetic Agents

Ephedrine

Pseudoephedrine

Phenylpropanolamine

Phenylephrine

Methylphenidate

Dextroamphetamine

Tyramine (with monamine oxidase inhibition)

Midodrine

Clonidine

Yohimbine

DL and L-dihydroxyphenylserine (DL-DOPS)

Nonspecific Pressor Agents

Ergot derivatives

Caffeine

Somatostatin analogues

β -Adrenergic Blocking Agents

Propranolol

Pindolol

Xamoterol

Prenalatorol

Prostaglandin Synthetase Inhibitors

Indomethacin

Flurbiprofen

Ibuprofen

Naproxen

Dopamine Blocking Agents

Metoclopramide

Domperidone

V1 and V2 Receptor Agonists

Desmopressin acetate (DDAVP)

Lysine-vasopressin

Erythropoietin

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