
CHAPTER 33

Orthostatic hypotension

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Background

Orthostatic (postural) hypotension (OH) is a frequent cause of syncope and may contribute to morbidity, disability and even death, because of the potential risk of substantial injury [1]. It may be the initial sign of autonomic failure and cause major symptoms in many primary and secondary diseases of the autonomic nervous system (ANS) (e.g. pure autonomic failure (PAF), multiple system atrophy (MSA), Parkinson's disease, dementia with Lewy bodies, pure autonomic failure, autoimmune autonomic ganglionopathy, amyloidosis, and diabetic autonomic neuropathy). It occurs frequently in elderly patients because of therapy (vasoactive drugs, dopamine and agonists, antidepressants), reduced fluid intake, and decreased ANS function. The prevalence of OH in patients 65 years and older has been reported to range from 5 to 30% [2]. In Parkinson's disease the prevalence of OH may be as high as 60% [3]. Characteristic symptoms of OH include light-headedness, visual blurring, dizziness, generalized weakness, fatigue, cognitive slowing, leg buckling, coat-hanger ache, and gradual or sudden loss of consciousness. Falls with injuries may result. However, a recent study demonstrated that one-third of patients with severe OH (blood pressure falls > 60 mmHg systolic) are asymptomatic during head-up tilt test [4].

Orthostatic hypotension is defined by consensus as a fall in blood pressure (BP) of at least 20 mmHg systolic and/or 10 mm Hg diastolic within 3 min in the upright

position [5]. This reduces perfusion pressure of organs, especially above heart level, such as the brain. Neurogenic OH results from impaired cardiovascular adrenergic function. The lesion can be postganglionic as in PAF, or preganglionic as in MSA. Other causes of OH are low intravascular volume (blood or plasma loss, fluid or electrolyte loss), impaired cardiac function due to structural heart disease, and vasodilatation, due to drugs, alcohol, heat [1].

Objectives

Orthostatic hypotension is an under-diagnosed disorder. Many new treatment options, pharmacological and non-pharmacological, have been published in recent years. Evidence-based guidelines for clinical and laboratory diagnostic work-up, and therapeutic management of OH are provided for physicians involved in the care of such patients.

Methods

Electronic search strategies used the following databases: Cochrane library, MEDLINE, Pub Med, and various internet search routines, for English publications. Key search terms included 'orthostatic hypotension', 'syncope', 'hypotension' and 'therapy', 'treatment', and 'diagnosis', and first-year availability of each referenced literature database until October 2009. References classified by evidence levels were selected by one individual and checked by another investigator. Where there was a lack of evidence but consensus was clear, we have stated our opinion as Good Practice Points (GPP) [6].

Diagnostic strategies

Tests to investigate OH are considered here and not general investigations of the ANS. A limitation is a paucity of randomized and blind studies. The wide variation of test methods, protocols, and equipment in autonomic laboratories make comparison of results difficult [7].

The history is of particular importance and has a high diagnostic value (pre-existing disease, detailed description of sequence of symptoms). The initial clinical evaluation should include a detailed physical and neurological examination, 12-lead ECG recording, routine laboratory testing, and BP measurements while supine and upright. Non-neurogenic causes of OH must be considered, as they can exacerbate neurogenic OH.

The cardiovascular responses to standing may be investigated by recording BP and heart rate while supine and for up to 3 min while upright. Passive head-up tilt testing (HUT) is recommended if the active standing test is negative, especially if the history is suggestive of OH, and in patients with motor impairment, as in Parkinson's disease, MSA, and spinal cord lesions. Tilt tables with foot board support, and if available, devices providing non-invasive, automatic, and ideally continuous heart rate and BP measurements are recommended [8].

Protocol:

- Orthostatic testing should take place in a quiet room, at a temperature between 20 and 24°C. The patient should rest while supine for ideally 5 min before HUT is started. Emptying the bladder before testing is recommended.
- Passive HUT to an angle between 60 and 80° for 3 min is recommended for the diagnosis of OH [9, 10].
- HUT is considered positive if systolic BP falls below 20 mmHg and diastolic BP below 10 mmHg of baseline. If symptoms occur, the patient should be tilted back to the supine position immediately.
- Measurement of plasma noradrenaline levels while supine and upright may be of value.
- In contrast with cardiologic guidelines pharmacological provocation with sublingual nitro-glycerine or intravenous isoproterenol is not recommended to diagnose OH as it reduces sensitivity and will result in false-positive outcomes [9].
- Combination of HUT and physiological measures, such as lower body negative pressure application, as used in neurally-mediated syncope, is not recommended for diagnosis of OH.

HUT is a safe procedure for the diagnosis of OH [11]. However, as syncope and arrhythmias have been described, the investigating staff should be adequately trained to recognize such problems. Resuscitation equipment and a team experienced in cardiac life support should be available at short notice (GPP).

Recommendations

All Level C

- Structured history taking.
- Detailed physical examination.
- 12-lead ECG recording.
- Routine laboratory testing.
- BP measurements while supine and upright.
- Cardiologic referral, if heart disease or abnormal ECG is present or suspected.
- Active standing or HUT, ideally with continuous assessment of BP and HR for 3 min.
- Further ANS screening tests, with other appropriate investigations, depending on the possible aetiology of the underlying disorder [1].

Management

Many new treatment options for OH have been studied in the past decade. Controlled trials have been performed for drugs and physical therapy. However, many of these studies included only small groups of patients with a variety of disorders that cause OH, and different diagnostic criteria have been used. If not noted otherwise, studies are classified as Class IV [6].

General principles

In addition to head up postural change, BP is influenced by many stimuli in everyday life. These include a hot environment, carbohydrate-rich meals, and exercise. The physiological mechanisms and individual strategies to avoid OH and syncope should be explained to the patients and caregivers. The following recommendations are mainly a result of panel consensus and qualified as GPP.

Elevated environmental temperatures, a hot bath or shower, and sauna should be avoided as they cause

venous pooling. Prolonged recumbence during daytime and sudden head-up postural change, particularly in the morning, when BP may be lowered by nocturnal polyuria, should be avoided [12]. Postprandial hypotension may increase OH (vasodilatation in splanchnic vessels). Large meals, especially carbohydrate-rich, and alcohol should be avoided. A carefully controlled and individualized exercise training (swimming, aerobics, and, if possible, cycling and walking) often improves OH.

Supine hypertension

Supine hypertension may be a problem, resulting from medication and/or being part of the disease. Therefore, 24 h measurement of BP is best before and if needed after starting a new therapy. Patients may self-monitor BP, daily at about the same time, and when they experience symptoms. Pressor medications should be avoided after 6pm and the bed head elevated (20–30 cm). On occasion, short-acting antihypertensive drugs may be considered (e.g. nitro-glycerine sublingual).

Non-pharmacological treatment

Avoidance of factors that may induce OH is recommended first line, particularly in mild forms. Educating the patients and carers on the mechanisms of OH is important. The next step includes a range of non-pharmacological strategies.

Patients should be advised to move to head-up position slowly, sit on the edge of the bed for some minutes after recumbence, and activate calf muscles while supine. Physical counter manoeuvres can be applied immediately at the onset of presyncopal symptoms. They need to be explained and trained individually. In case of motor disabilities and compromised balance, as in the cerebellar forms of MSA, programmes with appropriate aids have to be developed. Leg crossing with tension of the thigh, buttock, and calf muscles (party position), bending over forward to reduce the orthostatic difference between the heart and brain and compress the splanchnic vessels by increasing abdominal pressure, squatting to reduce blood pooling are effective in temporarily reducing OH [13–17]. Not all patients can perform these manoeuvres, and sitting or lying down, and using a cane that can be folded into a tripod chair [16], are useful. Elastic stockings and abdominal compression bands reduce venous pooling and have been shown to be effective in small studies [18, 19]. Sleeping with elevation of the head-end of the bed

(20–30 cm), particularly in combination with low dose fludrocortisone, improves OH [20].

To compensate for renal salt loss a liberal intake of salt, at least 8 g (150 mmol) of sodium chloride daily, if needed as salt tablets (starting dose 500 mg t.i.d.), are recommended. Water repletion (2–2.5 l/day) is important, while 500 ml of water is effective in raising BP immediately [21].

Cardiac pacing is not recommended in neurogenic OH [22].

Pharmacological treatment

Plasma expansion

Fludrocortisone

Fludrocortisone acetate is a synthetic mineralocorticoid with minimal glucocorticoid effects. It increases renal sodium reabsorption and expands plasma volume. Sensitization of alpha-adrenoceptors may augment the action of noradrenaline. After oral administration, fludrocortisone is readily absorbed and peak plasma levels are reached within 45 min. Elimination half-life is around 7 h.

Review of clinical studies No Class I and II studies were identified. One Class III [23] and one Class IV [24] study have shown an increase in BP and improvement of symptoms.

Recommendations

All Level C

- Fludrocortisone as first-line drug monotherapy of OH (0.1–0.2 mg per day).
- Full benefit requires a high dietary salt and adequate fluid intake.
- Combination of a high salt diet, head-up tilt sleeping (20–30 cm) and a low dose of fludrocortisone (0.1–0.2 mg) is an effective means of improving OH [20].

Mild dependent oedema can be expected and fludrocortisone should be used with caution in patients with a low serum albumin. Higher doses of fludrocortisone can result in fluid overload and congestive heart failure, severe supine hypertension and hypokalaemia [25]. To prevent hypokalaemia food rich in potassium such as fruits, vegetables, poultry, fish and meat is advisable. Headache may occur, especially while supine.

Alpha receptor agonists

There are many sympathomimetic drugs that act on alpha-adrenoceptors. Midodrine has been investigated extensively. Adrenaline (epinephrine) and noradrenaline (norepinephrine) are inactive when administered orally, and rapidly inactivated in the body after infusion. Common adverse effects of sympathomimetics with a central action such as ephedrine, are tachycardia, anxiety, restlessness, insomnia, and tremor. Dry mouth, impaired circulation to the extremities, supine hypertension, and cardiac arrhythmias may occur.

Midodrine

Midodrine is a prodrug with an active metabolite, desglymidodrine, that is a peripherally acting alpha-1-adrenoceptor agonist. It increases BP via vasoconstriction.

Midodrine does not cross the blood–brain barrier after oral administration and does not increase heart rate. The absolute bioavailability is 93% and the elimination half-life of desglymidodrine is 2–3 h. The duration of action of midodrine is approximately 4 h. It is excreted mainly in urine.

Review of clinical studies Class I: One dose-response study [26] and two studies with a total number of 259 patients investigating the efficacy, safety, and tolerability of long-term midodrine application [27, 28] were identified. An increase in orthostatic BP and decrease in OH-related symptoms were reported.

Class III: Efficacy and safety were higher with midodrine than with ephedrine [29].

Class IV: Midodrine reduced exercise induced OH in PAF [30].

Recommendations

All Level A

- Midodrine is recommended for mono- or combined therapy (e.g. with fludrocortisone).
- Initial dosage is 2.5 mg orally two to three times daily increasing gradually up to 10 mg t.i.d.
- Supine hypertension is a common (25%) adverse effect and may be severe. The last dose should be administered at least 4 h before going to sleep and BP should be monitored.
- Adverse effects are piloerection (goose bumps, 13%), scalp

or general pruritus (10 and 2%), scalp or general paraesthesia (9% each), urinary retention (6%), and chills (5%).

Some patients worsen on midodrine, maybe due to adrenoceptor desensitization [31]. It should be administered with caution in patients with hepatic dysfunction and is contraindicated in severe heart disease, acute renal failure, urinary retention, phaeochromocytoma, and thyrotoxicosis [32].

DOPS

Dihydroxyphenylserine (DOPS) is a prodrug which is converted by dopadecarboxylase to noradrenaline.

Review of clinical studies Class I: Administration of 200 mg and 400 mg L-DOPS daily improved OH symptoms in 146 chronic haemodialysis patients [33]. In short-term (4 weeks, $n = 86$) and long-term studies (24–52 weeks, $n = 74$) the efficacy of L-DOPS (400 mg/day) for OH after dialysis was demonstrated [34].

Class III: In 20 patients with familial amyloid neuropathy, L-threo-DOPS effectively improves orthostatic tolerance [35]. DL-DOPS improved OH in 10 patients with central and peripheral ANS disorders [36]. In 19 patients with severe OH, L-DOPS improved BP and orthostatic tolerance [37]. In 26 MSA and six PAF patients, the dosage of 300 mg twice daily L-threo-DOPS was effective in controlling symptomatic OH [38].

Recommendations

Level A

In a dosage between 200 mg and 400 mg per day, L-DOPS reduces OH. It is the only effective treatment of dopamine beta-hydroxylase deficiency. In all studies reviewed, no major side effects were reported. Future studies will have to investigate which patient groups benefit most from this drug.

Octreotide

The somatostatin analogue octreotide inhibits release of gastrointestinal peptides, some of which have vasodilatory properties. It is administered subcutaneously starting with 25–50 µg.

Review of clinical studies Four Class III studies were identified: In 18 PAF patients octreotide reduced postural, postprandial, and exertion-induced hypotension without

causing or increasing nocturnal hypertension [39]. Octreotide improved OH in MSA patients after acute and chronic administration [40, 41]. The combination of midodrine and octreotide was more effective in reducing OH than either drug alone [42].

Recommendations

Level C

Subcutaneous doses of 25–150 µg 30 min before a meal may be used to reduce postprandial OH. It does not increase supine hypertension. Nausea and abdominal cramps may occur.

Other treatment options

For the drugs listed below there is no clear evidence for use in OH. Many are recommended as GPP and warrant future studies.

Ephedrine, which acts on alpha- and beta-adrenergic receptors, is recommended by the authors, as it reduces OH in many patients, particularly with central lesions like MSA (15 mg t.i.d.). *Yohimbine*, an alpha-2-adrenoceptor antagonist with central and peripheral effects, has been used in refractory OH (6 mg daily) [43], Class III). Dihydroergotamine (DHE), a direct alpha-adrenoceptor agonist stimulating constriction of venous capacity vessels, has shown some benefit and may be used in severe OH (3–5 mg t.i.d. oral) (Level C: [44], Class III; [45], Class III; [46], Class IV). *Desmopressin*, a vasopressin analogue, acts on renal tubular vasopressin-2 receptors, diminishing nocturnal polyuria, and may be applied as nasal spray (10–40 µg) or orally (100–400 µg) at night [12], Class IV). *Erythropoietin* is recommended in anaemic patients [47–49], particularly in familial amyloidosis [50]. *Indomethacin*, a prostaglandin synthetase inhibitor, has been used in severe OH (75–150 mg/day) [51], Class IV, [43], Class III). *Pyridostigmine* may be effective in the treatment of OH through potentiation of sympathetic cholinergic ganglionic transmission, leading to increased vascular tone in the upright position [52]. In a double-blind, randomized, four-way crossover study the acute effects of 60 mg pyridostigmine bromide on supine and upright BP were tested against midodrine and placebo. Pyridostigmine significantly improved standing BP without worsening supine hypertension [53]. However, further studies on the

long-term efficacy and on possible adverse effects have to be performed before this treatment can be evaluated.

Summary

- OH is defined as fall in BP within 3 min of active standing or HUT.
- The key to managing OH is individually tailored therapy. The goal of treatment is to improve the patient's functional capacity and quality of life, preventing injury, rather than to achieve a target BP.
- Management of patients with OH consists of education, advice, and training on various factors that influence blood pressure, and special aspects that have to be avoided (foods, habits, positions, and drugs).
- Physical measures include leg crossing, squatting, elastic abdominal binders and stockings, and careful exercise (GPP).
- Increased water (2–2.5 l/day) and salt ingestion (>8 g or 150 mmol per day) effectively improve OH.
- Fludrocortisone is a valuable starter drug (0.1–0.2 mg per day, Level C). Second-line drugs include sympathomimetics, such as midodrine (start with 2.5 mg b.i.d and increase to 10 mg t.i.d, Level A) or ephedrine (15 mg t.i.d., GPP). DOPS (200–400 mg daily, Level A) reduces OH with only minor side effects. It is an effective treatment in dopamine beta-hydroxylase deficiency.
- Supine hypertension has to be considered.
- Individual testing with a series of drugs, based on the risk of side effects, pharmacological interactions and probability of response in the individual patient, may be considered when the measures shown here should not be satisfactory.

Need of update

These guidelines will be updated when substantial new data pertaining to the management of OH become available.

Conflicts of interest

The present guidelines were developed without external financial support. None of the authors reports conflicting interests.

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