Management of orthostatic hypotension in patients with Parkinson's disease

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ABSTRACT

Orthostatic hypotension is common in Parkinson's disease. The current recommended management of orthostatic hypotension related to Parkinson's disease involves first general measures and then medications with little risk of severe adverse side effects.

INTRODUCTION

Neurogenic orthostatic hypotension is common in patients with Parkinson's disease. Perhaps, 30%–40% of patients with Parkinson's disease have orthostatic hypotension, and the prevalence rises with age, disease severity and disease duration.[1 2] Orthostatic hypotension is defined as a drop in systolic blood pressure of ≥20 mm Hg or of diastolic blood pressure of ≥10 mm Hg, within 3 min of standing or upon head-up tilt (minimum 60°) on a tilt table.[3]

In patients with Parkinson's disease, autonomic degeneration impairs the sympathetic response to baroreceptor input.[4] During the course of Parkinson's disease, the accumulation of α-synuclein aggregates adds to the problems of neuronal degeneration and autonomic failure.[5] Upon standing, many patients with Parkinson's disease cannot compensate for the venous pooling and reduced venous return caused by their compromised autonomic reflexes. Their subsequent drop in blood pressure causes presyncopal symptoms and difficulty in maintaining an upright posture.

The management of orthostatic hypotension in patients with Parkinson's disease is important because minimising this problem can improve cognition, balance and quality of life.[6] Furthermore, treating orthostatic hypotension makes syncope less likely and so reduces the risk of falls and injury. Currently, the initial treatment is to remove iatrogenic causes (eg, antihypertensive medications) and to consider non-pharmacological interventions. Pharmacological interventions are needed only in a minority. In this review, we highlight both non-pharmacological and pharmacological options for managing orthostatic hypotension and analyse the extent to which these treatments help the problem.

TREATMENT

There are many therapeutic options for managing orthostatic hypotension in patients with Parkinson's disease. The currently recommended non-pharmacological (table 1) and pharmacological (table 2) treatment options are shown.

Non-pharmacological management

Water and salt

Drinking water and increasing salt intake increases plasma volume, which help to maintain blood pressure upon standing.

Table 1 Conservative treatments for orthostatic hypotension

Treatment	Recommended dose based on clinical trials
Increased salt intake	6–10 g daily
Increased water intake	1.5–2.0 L daily
Compression stockings	Knee-length compression: 40 mm Hg Thigh-length compression: 30 mm Hg Full-length compression: 20–60 mm Hg (from abdomen to ankle) Abdominal compression: 20–40 mm Hg

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Table 2 Pharmacological treatments for orthostatic hypotension

Treatment	Recommended dose based on clinical trials
Fludrocortisone	0.1–0.2 mg daily
Midodrine	10 mg three times daily
Droxidopa	100–300 mg three times daily
Pyridostigmine	To be determined upon further trials
Domperidone	To be determined upon further trials
Yohimbine	To be determined upon further trials

The recommended daily intake of water is 1.5–2.0 L/day and of sodium chloride is 6–10 g.[7] The salt may be incorporated into meals or taken as supplement tablets.

Increasing fluid intake has been shown to have a positive effect comparable to that of orthostatic hypotension medications[8 9] and has only mild adverse outcomes (eg, urinary frequency). High-salt intake, on the other hand, must be monitored carefully because it may lead to cardiovascular complications and mortality.[10]

Compression stockings

The rationale for compression therapy is to reduce venous pooling in the lower extremities, to promote venous return and cardiac output. The categories of compression stockings include knee-length, thigh-length, full-length and abdominal compression. The current literature reports modest efficacy and inconsistencies in the degree and location of compression.

Table 3 summarises the effect of compression on postural drop in patients with orthostatic hypotension at baseline. Five of 14 patients with neurogenic orthostatic hypotension reported mild symptomatic relief with knee-length compression despite insignificant changes in blood pressure.[11] Patients using thigh-length compression also reported modest symptom improvement.[12] While abdominal compression appears to be the only treatment capable alone of significantly reducing orthostatic hypotension, full-length compression also significantly reduces postural drop. In the self-reported Special Symptom Scale questionnaire for Orthostatic Intolerance, patients reported relief of dizziness, weakness, visual disturbance and palpitation when using elastic lower limb stockings (hip 30–40 mm Hg to ankle 40–60 mm Hg) after wearing them for 1 month.[13]

Although compression stockings provide orthostatic relief, there may be difficulty with compliance. Full-length compression stockings are uncomfortable and may be a burden to put on and wear. If the patient is able to comply, compression stockings should be incorporated in the treatment regimen for orthostatic hypotension. Ideally, abdominal compression should also be included because there is often considerable pooling in the splanchnic circulation.[15] In our experience, patients prefer compression stockings that do not cover the feet.

Pharmacological management

In most cases, pharmacological treatments are coadministered with non-pharmacological treatments. While medications can quickly alter blood pressure levels, their use needs careful monitoring to minimise adverse outcomes, particularly supine hypertension.[16]

Fludrocortisone

Fludrocortisone acts as a systemic corticosteroid, increasing sensitivity to circulating catecholamine.[17] When increasing water and salt intake is ineffective, fludrocortisone is the usual alternative way to increase plasma volume. Because fludrocortisone acts by intravascular volume expansion, its pressor effect is gradual. Fludrocortisone elevates both standing systolic and diastolic blood pressure,[12 18] decreases orthostatic symptoms[19] and lengthens the period that patients can stand without orthostatic symptoms.[12]

Fludrocortisone, primarily used for adrenocortical insufficiency in both the USA and Europe, is a first-line monotherapy agent to manage orthostatic hypotension. The recommended dose is 0.1–0.2 mg/day, and it can take up to 5 days to see the full effects. Higher doses elevate circulating epinephrine, which can cause hypokalaemia and supine hypertension. Fludrocortisone is not recommended for patients with congestive heart failure or chronic renal failure.

Midodrine

Midodrine, a peripheral α-1 adrenoceptor agonist, exerts a pressor effect on both venous and arterial

Table 3 Effect of compression stockings on postural drop in patients with orthostatic hypotension

	Reference	n	Applied pressure (mm Hg)	Change in postural drop (mm Hg)*
Knee-length compression	Denq *et al*[11]	14	40	–
Thigh-length compression	Schoffer *et al*[12]	17	30	–
Full-length compression	Denq *et al*[11]	14	40	+26.3
	Podoleanu *et al*[13]	21	20–60 (abdomen–ankle)	+18
Abdominal compression	Denq *et al*[11]	14	40	+12.4
	Smit *et al*[14]	9	20	+9

*Difference in the change in systolic blood pressure (SBP) from supine to standing position: $(SBP_{upright}–SBP_{supine})_{without\ compression}–(SBP_{upright}–SBP_{supine})_{compression}$.
+ indicates significant improvement with compression; – indicates no significant difference.

constriction[20] and is effective 1 h after ingestion.[21] The recommended dose (typically given in the morning, noon and afternoon to avoid supine hypertension in the evening) is up to 10 mg three times daily; each dose typically lasts for 4 h, consistent with blood levels of the active metabolite desglymidodrine.[22]

In double-blind studies, midodrine gave a dose-dependent increase in mean standing systolic blood pressure and resulted in significantly higher mean global improvement of orthostatic symptoms scores compared with placebo.[21 22] Midodrine's major limitation is supine hypertension but this adverse reaction may be minimised by taking it immediately before starting upright activities and avoiding it before becoming supine. Other potential side effects include piloerection, itchiness and urinary retention.[23]

In 2010, the US Food and Drug Administration (FDA) almost withdrew midodrine due to limited postmarketing trials. However, patient and physician lobbying proved successful in reversing the FDA's decision. Currently, midodrine is one of the two antihypotensive drugs approved by the US FDA. In the UK, midodrine is currently not licensed for managing orthostatic hypotension but is considered a second-line drug that may be used either as monotherapy or combined with fludrocortisone. Despite moderate quality of evidence in meta-analyses, subjective reporting on midodrine appears to be compelling enough to maintain midodrine as a therapeutic option. Ongoing clinical trials are currently being conducted to examine its long-term efficacy.

Droxidopa

Droxidopa (L-*threo*-dihydroxyphenylserine) is a synthetic prodrug that is converted into norepinephrine by the ubiquitous enzyme dopa-decarboxylase. In numerous trials conducted in Japan and Europe, droxidopa decreased postural drop in patients with orthostatic hypotension.[24 25] Smaller studies and clinical trials in the USA also showed that droxidopa reduced orthostatic symptoms.[26 27] In a recent phase III clinical trial, droxidopa improved Orthostatic Hypotension Symptom Assessment and Orthostatic Hypotension Daily Activity Scale in patients with neurogenic orthostatic hypotension.[28] In a double-blind study with 225 patients with Parkinson's disease, droxidopa treatment increased standing systolic blood pressure, reduced dizziness upon standing and reduced the number of falls.[29]

An open-label study reported that droxidopa was safe and well tolerated by patients with symptomatic neurogenic orthostatic hypotension.[30] Furthermore, it did not significantly increase supine blood pressure in the evening, thereby minimising the risk for supine hypertension overnight.[31] Due to its high tolerance and efficacy in improving orthostatic hypotension with a lower risk of supine hypertension, droxidopa has become a promising agent for managing orthostatic hypotension in patients with Parkinson's disease. Earlier this year, the US FDA approved droxidopa as an antihypotensive agent under the accelerated approval programme. Although droxidopa is still undergoing phase III clinical trials in Europe, growing evidence behind its efficacy supports its use as an alternative to fludrocortisone and midodrine.

The US FDA-recommended dose is 100 mg three times daily, although a dose titration study has reported 300 mg three times daily to be the optimal dosage.[25] Because patients with Parkinson's disease commonly take dopa-decarboxylase inhibitors to counter hyperdopaminergia induced by L-dopa treatment, dose adjustments for droxidopa may be required. However, the efficacy of droxidopa is not diminished when coadministered with the dose (25 mg for 100 mg L-dopa) of dopa-decarboxylase inhibitor typically used in the treatment of Parkinson's disease.[32]

Pyridostigmine

Pyridostigmine is a cholinesterase inhibitor that potentiates cholinergic transmission when the autonomic ganglia have already been engaged. Therefore, administering pyridostigmine as needed may mediate orthostatic hypotension without contributing to supine hypertension. Clinical trials to date have shown modest efficacy.

In an early open-label trial, 60 mg pyridostigmine orally increased standing blood pressure and reduced orthostatic symptoms in 15 neurogenic orthostatic hypotension patients.[33] A follow-up double-blind crossover study showed that pyridostigmine (60 mg) alone or coadministered with midodrine gave results consistent with the initial open-label trial.[34] Despite a modest increase in standing blood pressure, midodrine provided more salient symptomatic relief. One patient reported remission of symptoms after replacing midodrine with pyridostigmine.

While pyridostigmine offers a promising clinical benefit in the global improvement of orthostatic symptoms, the use of pyridostigmine as treatment is limited by undesirable side effects, including frequent abdominal cramping, nausea and vomiting.[35] It may, however, reduce constipation in patients with Parkinson's disease. We need further exploration in its mechanism of action, dose-dependent effects and long-term implications.

Domperidone

While dopamine agonists are widely used to manage Parkinson's symptoms, one major side effect is acute orthostatic hypotension after starting the treatment.[36] Domperidone is a peripheral dopamine D2 receptor antagonist that is effective in treating acute orthostatic hypotension induced by dopamine agonists.[37]

In one double-blind crossover study on patients with idiopathic Parkinson's disease, domperidone 10 mg three times daily was more effective than fludrocortisone in reducing postural drop.[12] The patients

taking dopamine agonists also preferred domperidone to fludrocortisone.

While domperidone appears a promising treatment of acute orthostatic hypotension induced by dopamine agonist therapy, its mechanism of action still remains to be elucidated. Domperidone is contraindicated in patients with underlying cardiac conditions because its use increases the risk of prolonged QT syndrome.[38]

Yohimbine

Yohimbine, an α-2 adrenergic antagonist, centrally activates the sympathetic response and promotes norepinephrine release.[39] This pressor effect enhances residual sympathetic tone.[40]

In an open-label trial, a 5.4 mg dose of oral yohimbine increased both seated and standing blood pressure.[41] The increase in the seated blood pressure was the greater. In a more recent crossover study that included Parkinson's disease cases, the same dose of yohimbine reduced lightheadedness and increased standing diastolic blood pressure.[42]

To enhance the pressor response in these patients, an alternative treatment may involve the coadministration of yohimbine with a norepinephrine transporter inhibitor. Atomoxetine selectively inhibits the norepinephrine transporter, thereby increasing synaptic norepinephrine concentration. Coadministering yohimbine with atomoxetine can then enhance the pressor effect of atomoxetine by potentiating the activity of the remaining sympathetic efferent fibres that have not yet degenerated. In a crossover study using 17 patients with severe peripheral autonomic failure, the combination of oral yohimbine (5.4 mg) with atomoxetine (18.0 mg) synergistically increased seated systolic blood pressure and improved orthostatic symptoms, whereas yohimbine and atomoxetine alone did not.[43] The results of this preliminary study are promising, but the duration of the pressor effects and safety of this treatment option require further study. While yohimbine is undergoing phase III trials in the USA, it is not recognised as an antihypotensive agent in Europe.

SUMMARY AND RECOMMENDATIONS

In our experience, managing orthostatic hypotension in patients with Parkinson's disease is clinically helpful because it improves their motor and cognitive function and further enhances their quality of life. Management of orthostatic hypotension should initially involve physiological countermeasures, such as reducing non-antihypertensive medication, increasing water and salt intake and compression therapy. If medications are needed, they may be selected based on symptom severity and side effect profile.

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