

THE SHEFFIELD AREA PRESCRIBING GROUP

Prescribing Guidelines for Use of Midodrine For Orthostatic (Postural) Hypotension

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Guidelines for the use of Midodrine in Orthostatic Hypotension

Statement of Purpose

This guidance has been written to support primary care clinicians in the management of patients taking midodrine

Introduction

Postural (orthostatic) hypotension is defined as a fall in blood pressure of over 20 mmHg systolic, (or 10 mm Hg diastolic), on standing or during head-up tilt to at least 60°. Symptoms include temporary loss of consciousness (TLoC), pre-syncope, dizziness and palpitations.

It may be a presenting feature in certain autonomic disorders (e.g. primary autonomic failure, diabetic neuropathy, reflex syncope, Postural Tachycardia Syndrome), or a pointer towards an alternative diagnosis (as in Multiple System Atrophy presenting with Parkinsonian features), and it may complicate drug therapy (as with levodopa and other dopaminergic treatments).

The incidence of postural hypotension increases with age and is more common in the over 75 age group.

Postural hypotension is associated with increased morbidity and also mortality, especially in elderly people due to falls resulting in injuries.

Midodrine is a prodrug which is converted to desglymidodrine and stimulates –alpha 1 adrenoreceptors. It improves orthostatic BP by increasing vasomotor and venomotor tone.

Indications for the purposes of this guideline –

Midodrine (licensed brand Bramox®) is indicated in adults for the treatment of severe orthostatic hypotension due to autonomic dysfunction when corrective factors have been ruled out and other forms of treatment are inadequate.

Postural hypotension caused by autonomic dysfunction can include patients with reflex syncope/vasovagal syncope; Postural Tachycardia Syndrome with a vasodepressor response; primary autonomic failure; Parkinsons / Multi System Atrophy. Physical (e.g. poor diet/ fluid intake) or pharmacological (e.g. drugs which cause the blood pressure to be lowered) causes of the postural hypotension should be ruled out.

Midodrine is recommended for the adjunctive treatment in the following circumstances:

Postural hypotension in those whose postural drop is 20 mmHg or more under the following conditions:

- When hypotension is due to an autonomic dysfunction as above.
- Only after non pharmacological measures are unsuccessful.
- Only after the recommended first line treatment, the mineralocorticoid fludrocortisone, has been tried or considered and found to be unsuitable.
- Midodrine may be added to ongoing fludrocortisone use. If the latter is not tolerated it would normally be withdrawn slowly. Withdrawal of corticosteroids after prolonged

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therapy must always be gradual to avoid acute adrenal insufficiency and should be tapered off over weeks or months according to the dose and duration of treatment. Careful monitoring is needed if fludrocortisone and midodrine are taken together (see drug interactions).

Midodrine treatment should be initiated by specialists but may be continued by general practitioners under this prescribing guideline.

Management of conditions causing postural hypotension

Initial management of conditions resulting in postural hypotension should be:

- Withdrawal / review of any drugs causing hypotension;
- Increasing clear fluid intake to at least 2 litres per day;
- Increasing salt intake to at least a teaspoon per day (6g) if not contra indicated;
- Advising and explaining to patients how to deal with their symptoms, and use of countermeasures;
- Providing written literature
PoTS UK <http://www.potsuk.org/> - [Living with Low Blood Pressure](#)
STARS <http://www.heartrhythmalliance.org/stars/uk> - Reflex Syncope, Causes of Low Blood Pressure in the Elderly
- Providing grade 2 (30mmHg compression at the ankle) compression tights/ stockings.

Medication / Dosage / Duration of treatments

Midodrine hydrochloride (Bramox®) - 2.5mg, 5mg tablet

Initial dose: 2.5 mg 2-3 times daily, increased if necessary at weekly intervals in small increments until an optimal response is obtained. Most patients are controlled at or below 30 mg daily given in divided doses. Doses in excess of 30 mg daily are not recommended. The use of midodrine should be stopped if supine hypertension increases excessively.

The manufacturers state that a 10mg dose would be expected to produce a rise in systolic blood pressure of approximately 15-30 mmHg.

Dosing of midodrine should occur during the daytime, when the patient is expected to be upright. Doses are usually at 4 hours intervals starting at (or up to 1 hour before) rising in the morning. Dosage may be changed to four doses 3 hourly if symptoms occur 3-3.5 hours after taking a dose. Last dose should be not later than 4 hours before bedtime to avoid supine hypertension.

Although there is no evidence to suggest that dosage requirements are different in the elderly, it is recommended that the initial dose used be small and that increases in dosage be titrated against the patient's clinical condition with caution.

Monitoring requirements

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It is essential to monitor supine and standing blood pressures during the use of the drug. Any supine hypertension may often be controlled by an adjustment in the midodrine dosage. Supine hypertension may also be controlled by elevation of the head.

We recommend use of 24 hr BP monitoring for every dose change and then once stable 24 hr BP monitoring yearly, plus a 12 lead ECG to screen for LVH.

The administration of midodrine should be stopped if the blood pressure in either position increases above 180/100 mmHg or is considered clinically significant. Patients with persistent labile blood pressure after stabilisation on midodrine should discontinue treatment.

Specialist hospital team/ secondary care responsibilities:

Initial non pharmacological interventions, as described above, should be adhered to before consideration of midodrine.

- The specialist team should review the patient to assess compliance and tolerance to the drug.
- A medication review should be carried out prior to starting the drug and any agents known or suspected to have contributed to postural hypotension stopped or reduced.
- U&Es, LFTs, FBC and 24hr urinary metanephrines/ catecholamines should be within normal limits.
- The aim of treatment is: to provide low risk therapy; ensure appropriate mobility and function; prevent blackouts/falls and associated trauma; and maintain a suitable quality of life.
- Reducing the postural blood pressure fall should not be the singular aim, as often there is dissociation between symptoms and the level of blood pressure.
- 24 hr BP monitoring should be arranged within the first 4 weeks of usage.
- The patient should be reviewed 4 weeks after starting midodrine.
- The patient should be asked to keep note of their symptoms during the first 4 weeks in particular:
 - have the episodes of transient loss of consciousness (T-LOC) reduced,
 - have episodes of pre-syncope and dizziness reduced,
 - if there are any symptoms, when do they occur in relation to taking midodrine.
- If the symptoms occur at about 3 – 3.5 hrs after taking the doses then ask the patient to take 4 doses of midodrine at 3 hourly intervals.
- The patient should be reviewed again at 4 weeks if a further dose adjustment is made, or 3 months if the dose is suitable.
- 24 hr BP should be checked after every dose adjustment.
- Supine or sitting BP should be checked at every clinic visit.

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- Monitor for any side effects.
- Once the patient is deemed stable on midodrine consider whether the prescribing could be taken over by the patient's GP.
- Advice should be given in young female patients that midodrine should be stopped if pregnant, breast feeding or the intention of becoming pregnant

General practice responsibilities:

Long term monitoring requirements

- Monitoring of supine BP when the patient is stable, according to the specialist's direction, usually every 3-6 months, or if symptoms recur.

To perform a supine BP the patient needs to be laid as flat as possible for at least 10 minutes. The arm should be horizontal and supported at the level of the mid-sternum because when the arm is below heart level this leads to an overestimation of systolic and diastolic pressures of about 10 mmHg. Correspondingly, raising the arm above heart level leads to underestimation of these pressures. If a standing blood pressure is to be performed also then the BP should be taken on immediate standing, at 1 minute and 3 minutes of standing.

Refer back to the clinic for advice if the BP falls outside normotensive ranges. Advice can be sought by contacting 0114 2269184.

- Assessment of symptoms, T-LoC, pre-syncope/ dizziness, according to specialist direction, usually every 3-6 months, or if symptoms worsen. Refer back to secondary care if worsening symptoms
- Yearly 24hr BP monitoring*
- Yearly ECG to monitor for LVH*
- Any queries about LVH to be referred back to specialist team
- Yearly U&Es and LFTs

*The 24 hr BP and ECG could be performed by secondary care if the patient lives within easy reach of the facilities; however, the patient's GP may be asked to perform these if this would be more convenient to the patient for them to be performed locally and the GP practice has the facilities for 24hr BP monitoring.

The drug should normally only be continued if benefiting the patient. If this is not apparent the GP should refer the patient to the specialist for review.

Patient/carer responsibilities

- To attend appointments in both secondary care and primary care for monitoring as requested.
- The patients should be cautioned to report symptoms of supine hypertension immediately such as chest pain, palpitations, shortness of breath, headache, blurred vision etc., If these symptoms present the patient should be advised to discontinue the medication immediately and seek advice.

Side effects/ Contraindications

A full list of side-effects / contraindications is given in the Bramox® summary of product characteristics (SPC).The details below are not a complete list and the BNF and the SPC remain authoritative.

Contraindications:

Midodrine is contraindicated in patients with

- hypertension,
- severe organic heart disease or congestive heart failure,
- pheochromocytoma
- thyrotoxicosis
- acute kidney injury
- severe renal insufficiency (creatinine clearance <30ml/min)
- urinary retention
- hyperthyroidism
- serious prostate disorder
- narrow angle glaucoma,
- obliterative or spastic vessel disease
- known hypersensitivity to any component of the product
- proliferative diabetic retinopathy

Precautions

Patients with a history of cerebrovascular accidents or with known risk factors for stroke should be monitored closely.

Cautions:

- Diabetes mellitus
- History of urinary retention
- Great caution should be exercised in patients with mild to moderate renal insufficiency (creatinine clearance > 30 mL/min and <90 mL/min)
- Slowing of the heart rate may occur after administration of midodrine, primarily due to vagal reflex, therefore great caution should be taken when using it together with other agents that directly or indirectly slow the heart rate e.g. digitalis, beta blockers, tricyclic antidepressants, phenothiazines and atypical antipsychotics. Patients experiencing any signs or symptoms suggestive of bradycardia (pulse slowing, increased dizziness, syncope, and cardiac awareness) should be advised to discontinue midodrine.
- The use of midodrine in patients who have an increased risk of or suffer from glaucoma / increased intra-ocular pressure or who are treated with mineralocorticoids / fludrocortisone acetate (which may increase intra-ocular pressure) should be avoided or monitored very closely.
- Treatment with midodrine in patients with liver impairment has not been studied. It is therefore recommended to monitor liver function before starting treatment with midodrine and on a continuous basis

Side effects: very common (>1/10) and common (>1/1000, < 1/10)

- **Nervous system disorders**
Common: paraesthesia of the scalp, headache
- **Vascular disorders**
Common: supine hypertension (dose dependent effect)
- **Renal and urinary disorders**
Very common: dysuria
Common: urinary retention
- **Gastrointestinal**
Common: nausea, dyspepsia, stomatitis
- **Skin**

Very common: piloerection, goosebumps, pruritus of the scalp
Common: pruritus, chills, flushing, rash

Common/significant drug interactions

- Sympathomimetic and vasopressor agents. The concomitant use of midodrine with vasoconstrictor, sympathomimetic pressor agents e.g. decongestants, including over the counter remedies, some appetite suppressants and other drugs such as methyldopa, tricyclic antidepressants, antihistamines, thyroid hormones and MAO-inhibitors should be avoided as this may cause excessive hypertension
- The effects of midodrine may be antagonised by α -adrenergic blocking drugs, such as prazosin and phentolamine. The concomitant use of alpha- and beta-receptor blocking agents (which reduce the heart rate) and midodrine requires careful monitoring.
- Glycosides - great caution should be taken when administering midodrine tablets to patients experiencing bradycardia produced by digitalis (or other glycosides) or psychopharmaceutical drugs since midodrine may potentiate reflex bradycardia and other kinds of conduction disorders or arrhythmias.
- Corticosteroid preparations - patients being treated with midodrine in combination with, mineralocorticoids or glucocorticoids (e.g. fludrocortisone) may be at increased risk of glaucoma/increased intraocular pressure, and should be carefully monitored. Midodrine may enhance or potentiate the possible hypertensive effect of corticosteroid preparations,

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be constituted for full information on contraindications, precautions, side effects and drug interactions.

Information for patients

Information on the main side effects and dosages and how to take the drug should be given in clinic.

The patient should be provided with PoTS UK patient information leaflet - [Midodrine](#)

Useful links / Additional information

- NICE advice – Orthostatic hypotension due to autonomic dysfunction: Midodrine (ESNM61) <https://www.nice.org.uk/advice/esnm61/chapter/Key-points-from-the-evidence>

References

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- Summary of product characteristics for Bramox®, accessed 26/07/2016:
<http://www.mhra.gov.uk/spc-pil/index.htm?prodName=BRAMOX%202.5%20MG%20TABLETS&subsName=MIDODRINE%20HYDROCHLORIDE&pageID=SecondLevel>
- Treatment of postural hypotension; J Neurol Neurosurg Psychiatry 1998; 65: 285-289.