THE SHEFFIELD AREA PRESCRIBING GROUP

Shared Care Protocol for Use of Midodrine for Orthostatic (Postural) Hypotension

Issue 2

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Shared Care Protocol for
Midodrine for Orthostatic (Postural) Hypotension

Statement of Purpose

This shared care protocol (SCP) has been written to enable the continuation of care by primary care clinicians of patients over the age of 16 years initiated on midodrine for the management of orthostatic (postural) hypotension by the cardiologists at Sheffield Teaching Hospitals FT, where this is appropriate and in the patients' best interests.

Users should be aware that this document is guidance on the management of a condition, not a commissioning arrangement. However, the number of patients receiving midodrine per general practice in Sheffield will be low.

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), or 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 alpha1-adrenoreceptors. It improves orthostatic BP by increasing vasomotor and venomotor tone.

Responsibilities of specialist clinician

- To discuss benefits and side effects of treatment with the patient/carer and obtain informed consent, in line with national guidance.
- To provide patient / carer with contact details for support and help if required.
- To initiate midodrine in appropriate patients: see Selection of patients and initial monitoring.
- To prescribe until patient stable as detailed under Selection of patients and initial monitoring.
- To contact patient's primary care prescriber to request prescribing and monitoring under shared care and send a link to or copy of the shared care protocol.

- To advise the primary care prescriber regarding continuation of treatment, including the duration of treatment.
- To discuss any concerns with the primary care prescriber regarding the patient's therapy.
- To participate in on-going monitoring as indicated here.
- The patient to normally remain under the specialists' care, but, exceptionally, if on-going specialist co-ordination of the patient's care is not required, an individual care plan should be agreed on a case-by-case basis.

Responsibilities of the primary care clinician

- To refer appropriate patients to secondary care for assessment.
- To contact the requesting specialist if concerns in joining in shared care arrangements.
- To continue to prescribe for the patient as advised by the specialist.
- Ensure monitoring as indicated in monitoring section below.
- Ensure women of childbearing potential are using contraception, where appropriate.
- To report any serious adverse reaction to the appropriate bodies e.g. MHRA and the referring specialist.
- To inform the specialist if the patient discontinues treatment for any reason.
- To seek the advice of the specialist if any concerns with the patient's therapy.
- To conduct an annual medication review with the patient or more frequent if required.
- In the event that the primary care prescriber is not able to prescribe, or where the SCP is agreed but the specialist is still prescribing certain items e.g. hospital only product; the primary care prescriber will provide the specialist with full details of existing therapy promptly by a secure method on request.
- For medication supplied from another provider, prescribers are advised to follow recommendations for Recording Specialist Issued Drugs on Clinical Practice Systems.

Responsibilities of Patients or Carers

- To be fully involved in, and in agreement with, the decision to move to shared care
- To attend hospital and primary care clinic appointments and to bring monitoring information e.g. booklet (if required). Failure to attend appointments may potentially result in the medication being stopped.
- To read the product information given to them.
- To take midodrine as prescribed.
- To present rapidly to the primary care prescriber or specialist should the clinical condition significantly worsen.
- To report immediately symptoms of supine hypertension 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.
- Report any suspected adverse effects to their specialist or primary care prescriber whilst taking midodrine.

- Inform the specialist, primary care prescriber or community pharmacist dispensing their prescriptions of any other medication being taken – including over-the-counter medication.
- Where appropriate, women of childbearing potential should use contraception and contact the specialist and GP if pregnant, breast feeding or has the intention of becoming pregnant.

Indication

Midodrine (licensed brand Bramox®, Midotense®) 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.

All other causes of postural hypotension should be ruled out including physical (e.g. poor diet/ fluid intake) or pharmacological (e.g. drugs which cause the blood pressure to be lowered) or endocrine.

Midodrine treatment should be initiated by specialists but may be continued by primary care clinicians under this SCP.

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 – see Information for patients;
- Providing grade 2 (30mmHg compression at the ankle) compression tights/ stockings.

Selection of patients and initial monitoring

This is the responsibility of the specialist.

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

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 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).

- 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, TFTs, vitamin B_{12}, ferritin, folate and vitamin D should be within normal limits.
- Early morning cortisol should be within normal limits or a short Synacthen® test undertaken to rule out adrenal insufficiency.

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.

The specialist team should review the patient to assess compliance and tolerance to the drug.

- 24 hr BP monitoring should be arranged within the first 6 weeks of usage.
- The patient should be reviewed 4 to 6 weeks after starting midodrine.
- The patient should be asked to keep note of their symptoms during the first 4 to 6 weeks in particular:
  - have the episodes of transient loss of consciousness (TLoC) 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 about 3 – 3.5 hrs after taking the dose, then ask the patient to take 4 doses of midodrine at 3 hourly intervals.
- The patient should be reviewed again after 4 to 6 weeks if a further dose adjustment is made, or after 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.
- 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 that women of childbearing potential should use effective contraception and that midodrine should be stopped if pregnant, breast feeding or has the intention of becoming pregnant.

Contra-indications

The details below are not a complete list and the current BNF and the SmPC remain authoritative

Midodrine is contraindicated in patients with:

- hypertension
- severe organic heart disease (e.g. aortic aneurysm, bradycardia, cardiac conduction disorders)
- congestive heart failure
- phaeochromocytoma
- thyrotoxicosis
- acute kidney injury
- severe renal insufficiency (creatinine clearance <30mL/min)
- urinary retention
- hyperthyroidism
- serious prostate disorder
- narrow angle glaucoma,
- Serious obliterative blood vessel disease, cerebrovascular occlusions and vessel spasms, myocardial infarction
- 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
- Atherosclerotic disease especially with symptoms of intestinal angina or claudication of the legs
- 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. Patients experiencing any signs or symptoms suggestive of bradycardia (pulse slowing,

increased dizziness, syncope, and cardiac awareness) should be advised to discontinue midodrine.

- Concomitant treatment with sympathomimetics and other vasopressor agents, including drugs used for the management of ADHD, should be avoided (see drug interactions)
- 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

Pregnancy and breast feeding

Midodrine is not recommended by the manufacturers during pregnancy and breast feeding or in women of childbearing potential not using contraception.

Dosage

Midodrine hydrochloride (generic 2.5mg, 5mg tablet; Bramox® **-** 2.5mg, 5mg, 10mg tablet; Midotense® - 2.5mg 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 midrodine 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 3 to 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.

Side –effects

The details below are not a complete list and the current BNF and the SmPC remain authoritative

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

Interactions

The details below are not a complete list and the current BNF and the SmPC remain authoritative

- Sympathomimetic and vasopressor agents. The concomitant use of midodrine with vasoconstrictor, sympathomimetic pressor agents e.g. decongestants, including over the counter remedies, tricyclic antidepressants, antihistamines, thyroid hormones, drugs used for the management of ADHD, and MAO-inhibitors should be avoided as this may cause excessive hypertension.
- The effects of midodrine may be antagonised by alpha- 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 digoxin (or other cardiac glycosides) since midodrine may potentiate reflex bradycardia and other types 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.

Monitoring

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 only in hypertensive patients.

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:

See Selection of patients and initial monitoring section
For responsibilities for on-going monitoring, see Long term monitoring requirements below.

General practice responsibilities:

Long term monitoring requirements

- Monitoring of supine BP when the patient is stable, according to the specialist's direction, usually every 6 to 12 months, or if symptoms recur. Where 6 monthly monitoring is advised, this will alternate between the primary care clinician and the specialist. Self-monitoring of supine BP may be suitable for some patients; the GP practice should consider the monitoring option best suited to the individual patient.

  To perform a supine BP the patient needs to be laid as flat as possible for at least 5 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.

- Yearly 24hr BP monitoring

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

0114 2269184 or email: **potsandsyncopeservice@nhs.net**

- Assessment of symptoms, TLoC, pre-syncope/ dizziness, according to specialist direction, usually every 3-6 months, or if symptoms worsen. Refer back to secondary care if worsening symptoms.
- Patients are advised to report to the clinic immediately symptoms of supine hypertension such as chest pain, palpitations, shortness of breath, headache, blurred vision.
- Yearly ECG to monitor for LVH, if hypertensive. The number of patients on midodrine with hypertension is few; if 24 hr BP monitoring records hypertension, the ECG will usually be undertaken by the specialist service.
- Any queries about LVH to be referred back to specialist team
- Yearly U&Es and LFTs

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.

Additional information

Information for patients

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

The patient should be provided with patient information leaflet – Midodrine, available from:

https://www.potsuk.org/wp-content/uploads/2021/10/Midodrine_v_2_Jan_2016_formatted.pdf

Booklets and information sheets are available from STARS and POTS UK:

https://www.heartrhythmalliance.org/stars/uk/patient-resources

https://www.potsuk.org/

Re-Referral guidelines

Patients who are being treated on the advice of the secondary care team, but in exceptional circumstances are no longer being seen in that setting, may still need review should problems arise. The appropriate level of care and/or advice should be available from the secondary care team in a timely manner without requiring a new referral.

Ordering information

Midodrine tablets are available through usual pharmaceutical wholesalers.

Contacts for support, education and information

STH Syncope and Postural Tachycardia Syndrome (PoTS) Service
https://www.sth.nhs.uk/services/a-z-of-services?id=291&page=284

Tel: 0114 2269184

Email: potsandsyncopeservice@nhs.net

PoTS UK: information for GPs https://www.potsuk.org/gp_guide

See also Information for patients.

References

- NICE advice – Orthostatic hypotension due to autonomic dysfunction: Midodrine (ESNM61 Oct 2015**)** https://www.nice.org.uk/advice/esnm61/chapter/Key-points-from-the-evidence
- Summary of product characteristics for Bramox® and Midotense®, accessed 19/02/22 from: https://www.medicines.org.uk/emc/
- Treatment of postural hypotension; Mathias C and Kimber J J Neurol Neurosurg Psychiatry 1998; 65: 285-289 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2170249/
- Royal College of Physicians Lying and Standing BP Timeline 2017
- NHS England Responsibility for prescribing between Primary & Secondary/Tertiary Care (January 2018) https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

The manufacturer's summary of product characteristics (SmPC) and the current edition of the British National Formulary (BNF) should be consulted for full information on contraindications, precautions, side effects and drug interactions

It will be presumed by the referring specialist that the primary care team is operating under this shared care protocol. Should the primary care prescriber feel unable to act under this shared care protocol they should discuss with the specialist requesting the care in the first instance. If after discussion, they still feel unable to prescribe then the primary care clinician must notify the specialist in writing.

Version history

This issue updates 'Prescribing Guideline for the use of Midodrine in Orthostatic Hypotension' approved by APG February 2017; developed by:

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