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Midodrine for Autonomic Dysfunction in Cardiac Disorders

Amber Continuation Guideline

This guideline provides prescribing and monitoring guidance for Midodrine therapy in the treatment of autonomic dysfunction in cardiac disorders. It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Specialist responsibilities prior to transfer of prescribing

- Complete pre-treatment assessment
- Initiate treatment, assess response to treatment, and prescribe until the dose is stable (if patient is responding to treatment)
- Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly, especially with regards to supine hypertension.
- Provide copy of patient information leaflet and drug monitoring card where appropriate
- Provide clinical details of treatment to GP
- Be available to give advice to GP and patient during treatment

GP responsibilities summary

- Prescribe medication as recommended below, once transfer of prescribing is complete
- Ensure all monitoring is completed in accordance with 'on-going monitoring' section.
- Monitor patient for adverse effects, contraindications and precautions as listed below.
- Take subsequent recommended actions as outlined below, including referral back to specialist if appropriate.

Background for Use

There is a spectrum of cardiac disorders which involve autonomic dysfunction: vasovagal syndrome (VVS, also known as neurocardiogenic syncope); postural tachycardia syndrome (PoTS) and inappropriate sinus tachycardia (IST). Many features of these disorders can overlap. Some patients fall into one diagnosis whereas others can have a diagnosis that overlaps between disorders.

A major feature of VVS and PoTS is vasodilatation, due to orthostatic intolerance, leading to fainting, particularly if patients become bradycardic. In PoTS there is a reflex tachycardia in response to the vasodilatation which may prevent fainting but causes palpitations and other problems. In IST there is a sinus tachycardia without vasodilatation.

Patients with these conditions have for a number of years been referred either via their GP or from other consultants to the electrophysiological (EP) cardiologists for assessment.

Treatment of these conditions depends on the predominating symptoms and patients respond differently to treatments.

• Midodrine is used for orthostatic intolerance in VVS and PoTS but rarely for IST, as this is not the major symptom.
• Fludrocortisone is sometimes used for VVS, but less often for PoTS as it is not very effective (clinical experience).
• Beta blockers are used for IST where the predominating symptom is tachycardia and sometimes for VVS but not often used for PoTS as can cause worsening of symptoms such as tiredness and lethargy.
• Ivabradine may also be used for palpitations, mainly in IST and sometimes in PoTS but not in VVS.

Midodrine has been used in clinical practice for a number of years by the EP cardiologists to treat mainly VVS or PoTS, and rarely IST. A licensed midodrine preparation is now available, it is indicated for the treatment of severe orthostatic hypotension due to autonomic dysfunction, but is not specifically licensed for PoTS.

Patients are started on a low dose usually 2.5mg or 5mg three times a day. Patients are re-assessed after 1 to 2 months and if symptoms have improved and the treatment is tolerated, treatment is optimized with upward dose titration if clinically indicated. Most patients are stabilized on 5mg three times a day but some require a higher dose in the morning e.g. 7.5mg. If patients do not report any improvement, even after dose escalation, treatment is discontinued. Many patients present with symptoms in early adulthood and continue treatment for a number of years. The condition often improves as the patient get older and treatment is gradually weaned off.

Previously midodrine treatment has been prescribed and supplied by OUH, as it was only available as an unlicensed import. Currently there are about 15 patients receiving treatment. In general 1 or 2 new patients are initiated on treatment per year and 1 or 2 may stop treatment. For the OUH formulary application for the licensed midodrine product it is estimated that the potential maximum number of patients per year would be about 20 within Oxfordshire population.

Supporting Information
Useful information sources

- **Summary of Product Characteristics:**
  Midodrine 2.5mg tablets
  Midodrine 5mg tablets
  Patient Information Leaflet - Midodrine

- **NICE evidence summary ESNM 611**
  Orthostatic hypotension due to autonomic dysfunction: midodrine
  https://www.nice.org.uk/guidance/esnm61/resources/orthostatic-hypotension-due-to-autonomic-dysfunction-midodrine-pdf-1502681100183493

- The POTS UK website is a very informative source for patients and healthcare professionals and sets out current evidence and treatment for POTS at www.potsuk.org/

Contraindications and Precautions

Contra-indications Action: stop drug and contact cardiologist	**Precautions** Action: contact cardiologist, consider reducing dose
• Severe organic heart disease e.g. bradycardia, MI, heart failure, aortic aneurysm, cardiac conduction disturbances • Hypertension • Stroke, severe vascular disease • Acute kidney disease, severe renal impairment (CrCl less than 30ml/min) • Serious prostate disorder • Urinary retention • Proliferative diabetic retinopathy • Phaeochromocytoma • Hyperthyroidism • Narrow angle glaucoma • Pregnancy (no data on safety) use under specialist only • Breastfeeding (no data on excretion into human milk)	• Severe orthostatic hypotension with supine hypertension. If supine hypertension occurs, ensure patient taking last daily dose at least 4 hours before bedtime and reduce the dose. If no improvement stop midodrine treatment. • Prostate disorders – midodrine may cause urinary retention • Renal and hepatic impairment – evaluate kidney and renal function on a regular basis (recommend yearly or more frequently if cause for concern) • Bradycardia due to vagal reflex – caution if other heart rate lowering medicines are initiated - discuss with cardiologist • Caution in patients with atherosclerotic disease e.g. claudication of the legs, intestinal angina

Dosage

Indication	**Dose**
• Vasovagal syncope • Postural tachycardia syndrome • Inappropriate sinus tachycardia (rarely)	For all indications: Initial dose 2.5mg or 5mg three times a day. Increase dose as needed to control symptoms Larger dose may be needed in the morning. Maximum dose 10mg three times a day (30mg total daily dosage) Sometimes dosage may be given four times a day if patients are experiencing breakthrough symptoms towards the end of the dosage interval. Last daily dose must be taken at least 4 hours before bedtime to prevent supine hypertension.

Time to Response

Time to response can vary between patients, depending on severity of initial clinical symptoms. Generally patients will notice improvement is symptoms within first few weeks. Response to treatment is mainly assessed subjectively as patients often present with a complex picture of symptoms.

Pre-Treatment Assessment
Assessment of patient's general symptoms e.g. dizziness, light-headiness, pre-syncope, syncope, palpitations, tiredness, weakness, shakiness, sleep patterns etc., so that response to treatment can be assessed.
Specific assessment for midodrine therapy:

- Lying and standing blood pressure (BP) and heart rate (HR).
- Biochemistry to assess renal function and thyroid function if not recently tested

Ongoing Monitoring
Check BP periodically during treatment - suggestion twice a year. If the GP, in consultation with the cardiologist, prescribes a change dose of midodrine, especially an increase in dosage, monitor BP, ideally within first few days of patient taking the new dosage. BP should be monitored in a sitting/standing position. However if BP is near upper limits of normal range BP should also be checked in a supine position. Annual biochemistry check (renal and hepatic function).

Treatment Discontinuation
The condition can improve over time and patients may not need to stay on life long treatment. For patients who have ongoing cardiology follow-up, treatment will be reviewed at the follow-up appointments by the cardiologists (usually annually). If a decision is made to trial a period off treatment with a view to stopping, treatment would usually be weaned slowly, under consultant guidance. For patients who may have been discharged from cardiology and have been on treatment for a number of years, the GP can contact the cardiologist for advice about stopping at any time, as guided by the patient's reports on their general symptoms. These patients, due to the complex nature of their condition, often see their GP regularly providing opportunity for discussion and review of ongoing treatment.

Patients may express a wish to discontinue treatment if unable to tolerate side effects despite dosage reduction, such as piloerection or pruritus/paraesthesia of the scalp (see below). In this situation GPs can contact the cardiologist for advice about stopping treatment and discussion on weaning doses. If the GP has any concerns about the development of supine hypertension, contact the cardiologist for advice about dosage reduction or stopping treatment depending on the BP measurements.

Actions to be taken
For advice contact the relevant cardiologist who initiated midodrine (see email list below). Alternatively, if urgent, contact the cardiology SpR on call on 0300 304 7777 bleep 4205.

Side Effects	**Action**
Supine hypertension (common)	Check timing of last dose – ensure dose is taken at least 4 hours before bedtime. Contact cardiologist for advice and consider dosage reduction.
Paraesthesia of scalp, pruritus of the scalp (comm on)	Consider dosage reduction if symptoms affecting quality of life
Piloerection – goose bumps (common)	Consider dosage reduction if symptoms affecting quality of life

Dysuria / Urinary retention (common)	Consider dosage reduction if symptoms affecting quality of life
Nausea, dyspepsia, stomatitis (common)	Consider dosage reduction if symptoms affecting quality of life
Sleep disturbances, restlessness, agitation, irritability (uncommon)	Consider dosage reduction if symptoms affecting quality of life
Bradycardia due to vagal reflex (uncommon)	Consider dosage reduction if clinically indicated
Urge to urinate (less common)	Consider dosage reduction
Raised hepatic function tests (rare)	Contact cardiologist for advice consider dosage reduction / stopping midodrine depending on severity
Tachycardia, palpitations (rare)	Contact cardiologist for advice consider dosage reduction / stopping midodrine depending on severity

Notable Drug Interactions (Refer to BNF and SPC)

- Avoid concurrent use with sympathomimetic agents including those contained in OTC cold and flu remedies and decongestant products e.g. phenylephrine, xylometazoline, methyldopa, clonidine. Also illicit use of amphetamines and cocaine should be avoided.
- Avoid concurrent use of other vasoconstrictive substances such as tricyclic antidepressants, thyroid hormones, MAO-inhibitors, antihistamines, reserpine, guanethidine
- Avoid alpha adrenergic antagonists as the effect of midodrine will be blocked e.g. prazosin, phentolamine
- Use with caution any drubs that directly or indirectly slow the heart rate e.g. digoxin, beta blockers.
- Corticosteroid preparations may potentiate or enhance the hypertensive effect of midodrine. If patients are being treated with midodrine in combination with mineralcorticosteroids or glucocorticoids monitoring BP is necessary at start of therapy. This would be initially managed by cardiologist until patient is stable. Patients may also be at increased risk of glaucoma / increased intraocular pressure.

Back-up Information and Advice

Contact the relevant Consultant Cardiologist responsible for the patient's care, this will be one of the electrophysiological (EP) specialists.

EP Consultant cardiologists	**Contact Details**
Dr Yaver Bashir	Yaver.bashir@ouh.nhs.uk
Dr Tim Betts, Consultant cardiologist	Tim.betts@ouh.nhs.uk
Dr Mathew Ginks Consultant	Matthew.ginks@ouh.nhs.uk
Dr Kim Rajappan	Kim.rajappan@ouh.nhs.uk

References

See supporting information for useful information sources.

Other information which may be useful:

- Blair P and Grubb MD. Postural Tachycardia Syndrome. Circulation 2008; 117: 2814-2817
- Perez-Lugones et al. Usefulness of midodrine in patients with severely symptomatic neurocardiogenic syncope: A randomized controlled study. J Cardiovasc Electrophysiol 2001; 12: 935-938.