NHS LINCOLNSHIRE in association with
UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE: UNLICENSED MEDICINE - MIDODRINE for the treatment of ORTHOSTATIC HYPOTENSION and VASOVAGAL SYNCOPE

General Principles

Shared Care Responsibilities:
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 60, September 2010, pg.2)

Aims:
(1) The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

(2) Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

(3) Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

(4) Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies

Further copies of any guidelines in this series are available from PCT Prescribing Advisers.

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Drug Details

Approved Name: **Midodrine**
Brand Name: Gutron manufactured by Nycomed Austria (imported via IDIS)
Form and Strength: 2.5mg and 5mg tablets

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Send a letter to the GP suggesting that shared care is agreed for this patient.
2. Ensure that the patient receives initial supplies of midodrine from the hospital until the GP formally agrees to share care.
3. Carry out U&E's, LFTs before commencing therapy and will communicate this to the GP.
5. Obtain informed consent from the patient on the use of an unlicensed medicine and provide patient with pre-treatment information leaflet.
6. Periodically review the patient's clinical condition and monitor response to treatment regularly.
7. Communicate promptly with GP when treatment changes.
8. Provide support to the GP and advice if treatment needs to be discontinued.

GP Responsibilities

The GP will:

1. Notify the consultant in writing, without undue delay, if they agree to share care.
2. Monitor the patients overall health and wellbeing.
3. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interaction.
4. Prescribe the medication for the patient.
5. Carry out monitoring tests: Blood pressure checks (supine and standing) every month; U&E/creatinine every 3 months; LFTs every 6 months or at intervals agreed with consultant.
6. Refer back to the specialist if condition deteriorates as advised by specialist service.
7. Report adverse events to specialist and CSM through yellow card system where appropriate.
8. Discontinue treatment (where necessary) on the advice of the specialist.

Referral Criteria

1. Patients will have received at least 3 months of midodrine therapy on hospital prescription.
2. Patients will have been stabilised on a suitable dose of midodrine.
3. The specialist will have carried out an assessment of efficacy.

Licensed Indications

Midodrine is unlicensed. It is used for the treatment of idiopathic orthostatic hypertension when conventional (licensed) preparations such as fludrocortisone have failed.

Recommended Dosage and Administration

Adults and Adolescents: Treatment with midodrine should be started under close medical supervision. Hourly measurements of blood pressure (supine and sitting or standing, if possible) should be made for 3 hours following the first dose and also the second dose of a three times daily dosage regimen.

It is recommended that treatment begin at the lowest level and be titrated at intervals of 3 to several days until the optimal response is obtained. Upon escalating the dosage, the supine and standing blood pressure should be closely monitored in hospital, in clinics as for the initiation of therapy, hourly for 3 hours following the first 2 doses.

The usual starting dose is 2.5mg 3 times daily. Single doses of 2.5, 5 and 10mg have been successfully employed. Most patients are controlled at or below 30mg/day given in 3 or 4 divided doses. Doses in excess of 40mg daily are not recommended**. The normal recommended maximum dose is 30mg daily**.
Midodrine can be given up to 6 times/day. Some patients require a morning dose that is higher than that taken later in the day.
In some instances midodrine has been given on a 3 times/day schedule as follows: 1 to 2 hours before arising in the morning, mid-morning and mid-afternoon.
In order to reduce the potential for supine hypertension, it is recommended that the last dose of midodrine is given at least four hours before bedtime.

Background Pharmacology

Midodrine is a postsynaptic alpha adrenergic receptor stimulant with little effect on the beta-adrenergic receptors in the heart. The actions of midodrine on the cardiovascular and other organ systems are essentially identical with those of other alpha-adrenergic receptor stimulants, such as phenylephrine or methoxamine. The most prominent effects of midodrine are on the cardiovascular system, consisting of a rise in systolic and diastolic blood pressures, accompanied by a marked reflex bradycardia. The increase in blood pressure is due almost entirely to an increase in peripheral resistance. Midodrine slightly decreases cardiac output and renal blood flow; it increases the tone of the internal bladder sphincter and delays the emptying of the bladder.
Midodrine is a prodrug, i.e. the therapeutic effect of orally administered midodrine is due to and directly related to its conversion after absorption to desglymidodrine which differs chemically from methoxamine only by lacking in a methyl group on the side chain.

Preparations Available

Midodrine is available as tablets containing 2.5mg and 5mg of midodrine.

Adverse Effects

Supine hypertension

The most serious and frequent adverse reaction to midodrine in patients suffering from primary neurogenic hypotension is the unacceptable elevation of supine arterial blood pressure which, if sustained, may cause stroke, myocardial infarction, congestive heart failure, renal insufficiency. Symptoms of supine hypertension are more frequently detected at the initiation of midodrine therapy and during the titration period.

To minimise the incidence of supine hypertension, instruction how to initiate midodrine therapy should strictly be followed. Patients should be cautioned to report symptoms of supine hypertension immediately. Symptoms may include cardiac awareness, pounding in the ears, headache, blurred vision, etc. If these occur, the patient should discontinue the drug and consult with the prescribing physician.

Other adverse effects:
Cardiovascular system – palpitations, tachycardia, reflex bradycardia, arrythmias.
Skin – parasthesia, rash, pruritis (mainly of the scalp) and flushing.
Gastrointestinal – nausea/dyspepsia, vomiting
Urinary – urinary retention, dysuria
Central Nervous System – headache, restlessness, excitability, irritability, light-headedness or dizziness.

Drug Interactions

When administered concomitantly with midodrine, cardiac glycosides may enhance or precipitate bradycardia, block or arrhythmia.

The use of drugs which stimulate alpha adrenergic receptors (e.g, phenylephrine, phenylpropanolamine or dihydroergotamine) may enhance or potentiate the pressor effects of midodrine. Therefore, when midodrine is used concomitantly with vasoconstrictor sympathomimetic agents, use caution.
Betablockers . Midodrine may enhance heart rate reducing effect of beta-blockers.
Patients on salt-retaining steroids (e.g. fludrocortisone), with or without salt supplementation, may experience an excessive pressor effect after midodrine therapy, especially in the supine posture. The possibility of hypertensive effects with midodrine can be minimised by either reducing the dose of fludrocortisone or decreasing the salt intake prior to initiation of treatment with midodrine.

Alpha adrenergic blocking agents antagonize the vasopressor effect of midodrine.
Atropine vascular contraction affect of midodrine is increased, heart rate-reducing effect of midodrine is lessened.

Precautions and Contraindications

Contra-Indications: patients with severe organic heart disease, hypertension, arrhythmias, acute nephritis, prostatic hyperplasia with formation of residual urine, urinary retention, phaeochromocytoma, thyrotoxicosis, hyperthyroidism, narrow angle glaucoma or known hypersensitivity to midodrine.

Precautions:

Urinary Retention: Midodrine may induce an increase in the tone of the internal sphincter of the urinary bladder which may lead to urinary retention. Midodrine also may affect the bladder trigone which may result in a delayed response to bladder filling. Patients should be told to report promptly any indication of urinary retention (e.g. hesitancy or frequency of micturition) which may be a sign of urinary retention. Midodrine should be used with caution in patients with urinary tract outflow obstruction, neurogenic bladder or similar conditions, since midodrine is eliminated by the kidneys and accumulation may occur in such patients.

When midodrine is used concomitantly with other vasoconstrictor sympathomimetic pressor agents, monitoring of blood pressure is necessary.

Pregnancy: No teratogenic effects have been observed in studies in animals. There are no data on the use of midodrine on pregnant women. Therefore, midodrine should be used during pregnancy only when the benefit to the mother exceeds the possible harm to the foetus.

Lactation: It is not known if midodrine is excreted in human milk. Caution should be exercised when midodrine is administered to nursing mothers.

Children: Safety and effectiveness in children have not been established.

Monitoring

Baseline:

Blood pressure (supine and standing), U&E, creatinine, LFTs, .

Thereafter – Blood pressure (supine and standing) weekly for first 4 weeks and monthly thereafter. U&E/creatinine every 3 months. LFTs every 6 months.,or as instructed by specilaist team.

Treatment should be stopped and advice from the supervising specialist sought if:

- The patient complains of symptoms suggestive of supine hypertension (as noted above)
- Blood pressure rises above 160/100

Indication of Likely Cost of Therapy in Primary Care

5mg TDS 28 day cost £24.36.

Midodrine can be obtained from -

Mawdsley Brook Ltd
Unit 4, Crompton Road Business Park
Crompton Road
DONCASTER
DN2 4PW

Tel 0130 255 3000
Fax 0130 255 3003

Information Given to the Patient

Pre-treatment patient information leaflet.

Contact Details

Grantham Cardiology Team
Dr Houghton's Secretary (01476) 464791
Dr Houghton (01476) 464520 (or via pager)

References

Midodrine hydrochloride tablets. Upsher-Smith Laboratories INC. Revised 12/2006.
Midodrine (Gutron/Midon) Shared Care - based on MTRAC template

Authors

Dr A Houghton Consultant Cardiologist ULHT
Mr R Thompson Senior Pharmacist ULHT
Reviewed Mrs C.M. Johnson Interface Lead Pharmacist NHSL