Shared Care Guidance

Metolazone for the Treatment of Refractory Heart Failure

This shared care agreement outlines the way in which the responsibilities for managing the prescribing of metolazone 5mg tablets for the treatment of heart failure can be shared between Secondary Care and Primary Care colleagues.

Introduction:

Metolazone is a quinazoline diuretic, with properties generally similar to the thiazide diuretics. The actions of metolazone result from interference with the renal tubular mechanism of electrolyte reabsorption. Metolazone acts primarily to inhibit sodium reabsorption at the cortical diluting site and to a lesser extent in the proximal convoluted tubule. The drug can produce a profound diuresis when utilised with loop diuretics and so patients on metolazone treatment must be monitored carefully.

Patients reaching the clinical point when they need metolazone treatment will usually have been under the secondary care consultant cardiologist and community heart failure team for some time. The decision to treat with this specialist treatment will either be made during an in-patient hospital stay or via the community heart failure team following a conversation/discussion with the hospital consultant.

Indication:

Sanofi-Aventis discontinued the UK licensed metolazone preparation in 2012. Presently, metolazone is only available as an unlicensed special order imported product (Zaroxolyn®) that is indicated as a diuretic and antihypertensive.

Within the locality, the drug is approved for use in combination with a loop diuretic as a second line agent for the small number of refractory heart failure patients who have not responded to standard therapy at optimum dosage.

Dose & Administration:

The starting dose of metolazone is usually 2.5mg (half a 5mg tablet) once or twice weekly; with dose titration in accordance to clinical response and affect on blood urea and electrolytes.

Adverse Effects:

Side effects of metolazone are similar to the thiazide group of diuretics and include mild gastrointestinal disturbances, postural hypotension, altered plasma lipid concentration, metabolic and electrolyte disturbances. Less common side effects include blood disorders and impotence. The Zaroxolyn® product monograph[1] gives a full list of all metolazone-related adverse reactions.

Contraindications/Cautions:

Contraindications:

- Hypersensitivity to metolazone or to any of the excipients included with the medicinal form
- Refractory hypokalaemia
- Hyponatraemia
- Symptomatic hyperuricaemia
- Anuria

Special warnings/precautions:

- Diabetes and gout may be aggravated
- Hepatic Impairment
- Pregnancy
- Close monitoring of Urea and Electrolytes in renal impairment

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Drug Interactions:

- Hypokalaemia caused by metolazone can increase the cardiac toxicity of cardiac glycosides, flecainide, lidocaine, disopyramide and sotalol
- Hypokalaemia caused by metolazone increases the risk of ventricular arrhythmias with amisulpride, atomoxetine and pimozide
- Metolazone may reduce the excretion of lithium (leading to increased plasma lithium concentrations and the associated risk of toxicity)
- Enhanced hypotensive effect when diuretics are given with ACE inhibitors, alpha-blockers and angiotensin-II receptor antagonists
- Diuretics increase the risk of nephrotoxicity of NSAIDs
- Corticosteroids or ACTH Therapy: May increase the risk of hypokalemia and increase salt and water retention.

Monitoring Requirements:

Before treatment:

- Urea and electrolytes (U&Es) and creatinine

During treatment:

- Urea and electrolytes (U&Es) and creatinine within 7 days of starting treatment
- Recheck every 7–14 days, depending on the person's stability.
- Patients should be weighed or encouraged to self-weigh daily. Aim for a daily weight loss of 0.5 Kg.
- If diuresis is extensive, consider earlier testing of renal function.

Once treatment is stable:

- Measure renal function and serum electrolytes at least once every month
- Continue to monitor body weight

Parameters for Intervention:

Action to be taken if abnormal results/adverse effects are detected and this should be a shared care approach.

During normal working hours (Monday to Friday, 9am-5pm) the Community Heart Failure Team can be contacted to offer advice regarding clinical parameters and blood tests. Out-of-hours and over the weekend the prescriber may be required to make a clinical decision based upon the received blood results and clinical presentation of patient; or the relevant Consultant Cardiologist may be contacted for advice.

The following provides guidance for prescribers if abnormal results are picked up.

Weight Change:

- Daily weight loss in excess of approximately 0.5-1kg – consider reducing dose.

Creatinine levels and / or eGFR:

- If the serum creatinine level increases by more than 20% of baseline or the eGFR decreases by more than 15% of baseline - re-measure renal function within 2 weeks.
- An increase of serum creatinine less than 30% from baseline does not normally require action.
- If creatinine increases by 30–50% (or to greater than 200 micromol/L) or eGFR is less than 30 mL/min/1.73 m2 - review volume status and then reduce dose or stop diuretics (if the person is hypovolaemic). Re-measure renal function within 1 week.
- If creatinine increases by more than 50% or to greater than 256 micromol/L (eGFR approximately 20–25 mL/min/1.73 m2) - assess volume status, check blood pressure and review other renal function tests, including electrolytes and proteinuria. If the person is hypovolaemic, stop the diuretic. If there is any uncertainty, contact heart failure nurses / cardiologist urgently.

Potassium:

- If potassium level < 3 mmol/L (or 4 mmol/L in high-risk people), ensure patient is reviewed urgently to prevent potassium falling lower and requiring admission to hospital for urgent replacement. Consider increasing dose of ACE inhibitor or add spironolactone - discuss with heart failure team if available. If these options have been done give potassium supplements; for example, Sando K 24mmol (2 tablets) tds until potassium is >4mmol/l (usually for approximately 3 days and be aware that levels will continue to rise once supplements have been discontinued). Potassium levels should be rechecked on a 24- 48hourly basis until >4mmol/L. Then repeat U&Es within 7days.
- People at high risk of cardiac arrhythmias with even mild hypokalaemia include:
    - Those taking digoxin or drugs that prolong the QT interval (such as amiodarone).
    - Those with paroxysmal arrhythmias, unstable angina, or chronic liver disease.
    - If potassium concentration < 2.5 mmol/L (or <3.5 mmol/L in high-risk people) – seek urgent advice and consider admission to hospital for urgent potassium replacement.

Sodium:

- If a sodium level of <131mmol/L is reported, repeat level next day and contact heart failure nurses for advice as soon as results are available. Consider reduction in diuretic therapy if clinically stable.

Symptomatic Hypotension (Systolic pressure < 90 mmHg associated with dizziness, fainting, confusion):

- Check blood chemistry to exclude other causes for symptoms, consider reduction in diuretic therapy if clinically stable – discuss with heart failure nurses

Worsening Symptoms (increased dyspnoea, fatigue, oedema, weight gain):

- Contact heart failure nurses to discuss increasing dose

Shared Care Responsibilities:

Initiating Treatment Specialist (Consultant Physician or Community Heart Failure Team)

1. Confirm indication and need for metolazone therapy.
2. If Community Heart Failure Team initiation, capture in the medical notes that a conversation has taken place with the relevant Consultant confirming the clinical need.
3. Discuss the benefits and side effects of treatment with the patient and document that the patient has given informed consent to the unlicensed use of metolazone.
4. Prescribe treatment and ensure patient is stable before transfer to GP care.
5. Ensure baseline monitoring of urea-and-electrolytes profile, creatinine level and pre-treatment weight of the patient.
6. Ensure the patient is aware of the signs of over diuresis or worsening symptoms, when to seek medical advice from their GP and other professionals involved in the patient's care.
7. Review patient regularly to monitor the patient's disease and continued need for metolazone therapy
8. Promptly communicate with the General Practitioner any changes in treatment results of monitoring undertaken and assessment of adverse events.
9. Discontinue treatment if the patient experiences serious adverse effects or no longer requires treatment.
10. Report serious adverse events to the Committee on Safety of Medicines.

Ongoing Treatment Provider (General Practitioner)

1. Monitor patient's overall health and wellbeing.
2. Provide the patient with repeat prescriptions of metolazone once the specialist has recommended continuation therapy (i.e. when the patient is stabilised on therapy), noting that metolazone is an unlicensed drug and may take longer for community pharmacies to order in.
3. Ensure the patient is having regular monitoring as outlined earlier within this document.
4. Seek advice from the Specialist Heart Failure nurses or Consultant Physician if the patient's condition deteriorates or if there a change in the patient's status.
5. Discontinue therapy when necessary or if requested to do so; ensuring full communication with the initiator of the treatment.
6. Refer patient to the Specialist if his or her condition deteriorates.
7. Report serious adverse events to the Committee on Safety of Medicines.

Warning signs of electrolyte imbalance irrespective of cause are: dryness of mouth; thirst; weakness; lethargy; drowsiness; restlessness; muscle pains or cramps; muscular fatigue; hypotension; oliguria; tachycardia; and gastrointestinal disturbances such as nausea and vomiting.

Patient (and if appropriate, the carer):

1. Report to the Secondary Care Specialist or GP if he or she does not have a clear understanding of the prescribed treatment.
2. Ensure attendance for required blood testing.
3. Share any concerns in relation to treatment with metolazone.
4. Report any adverse effects and warning signs of electrolyte imbalance (as listed above) to the Secondary Care Specialist or GP; whilst taking metolazone therapy.
5. Weigh themselves regularly as requested by clinicians.
6. Ensure they report signs of over diuresis such as weight loss of more than 0.5kg – 1kg a day, any dizziness, light headedness, fatigue or uraemia; or any signs of worsening symptoms.

Contact Numbers for Advice and Support:

Colchester Hospital University NHS Foundation Trust	(01206) 747474 (Switchboard)
ACE Community Heart Failure team	(01255) 588016
• **Hayley Coxon. Community Cardiology Clinical Lead** *hayley.coxon@acecic.nhs.uk*	(01255 206244)
CHUFT Pharmacy Department	**(**01206) 742355
CHUFT Medicines Information Help Line:	(01206) 742161

References

(1) Product Monograph. Zaroxolyn® tablets – http://products.sanofi.ca/en/zaroxolyn.pdf

(2) Shared Care Guideline. Metolazone for Refractory Heart Failure (Adults). Wirral University Teaching Hospital http://mm.wirral.nhs.uk/document_uploads/shared-care/Metolazoneforresistantheartfailure.pdf

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