DEMECLOCYCLINE HYDROCHLORIDE

Demeclocycline Shared Care Guideline for the treatment of chronic hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

Introduction

The recommendation of the European guidelines[1] for the management of hyponatraemia is to avoid demeclocycline altogether in hyponatraemia due to insufficient evidence for benefit and reports of acute kidney injury. However in daily practice patients do respond to demeclocycline in some cases and with the limited options available demeclocycline may still have its use in hyponatraemia if the patient has not responded to fluid restriction.

Indication/Licensing information

For the treatment of chronic hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) secondary to malignant disease, where water restriction is ineffective and the patient does not have concomitant cirrhosis.[2]

Treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable.[3]

Dosage and administration

For the treatment of Chronic Hyponatraemia due to SIADH

Adults only

Initially: 900mg- 1200mg daily in divided doses

Maintenance dose: 600-900mg daily in divided doses

Demeclocycline should be swallowed whole with plenty of fluid while sitting or standing. Doses should be taken an hour before or 2 hours after meals as absorption of demeclocycline is impaired by milk and food.

Please note: Demeclocycline therapy in the treatment of chronic hyponatraemia due to SIADH should not be withdrawn without commencing other methods of control.

Responsibilities of the specialist initiating treatment[4]

- Perform baseline tests (**FBC, U&Es and LFTs**), repeat at least every 2 weeks until stabilised. The frequency of testing should be decided on an individual patient basis and in some patients testing may be required twice a week to start with. These tests will be the responsibility of the discharging specialist until the patient is seen in clinic.
- Discuss the benefits and side effects of treatment with the patient.
- Initiate and stabilise treatment with demeclocycline. Stabilisation will usually take 2 – 4 weeks.
- Ask the GP whether he or she is willing to accept prescribing responsibilities.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care (See Shared care request form in Appendix A).
- Prescribe and supply medication until care is transferred to GP.
- Ensure GP has access to blood results for information.
- Periodically review the patient's condition in clinic every 3 to 4 months and communicate promptly with the GP when treatment is changed.
- Repeat blood tests (**FBC, U&Es & LFTs**) every 3-4 months.
- Advise the patient and GP on when to adjust the dose or stop treatment.
- Advise GP on review, duration or discontinuation of treatment where necessary.
- Ensure that clear backup arrangements exist for GPs to obtain advice and support.
- If patient fails to attend for monitoring tests, inform GP and provide appropriate guidance (e.g. on stopping treatment)
- Report adverse events to the MHRA (via Yellow Card) https://www.gov.uk/report-problem-medicine-medical-device

Responsibilities of other prescribers[4]

Acceptance of Responsibility by the Primary Care Clinician
It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able.

- Reply to the request for continuing prescribing soon as practicable preferably within 2 weeks.
- Prescribe demeclocycline at the dose recommended once patient is established on treatment.
- Monitor patient's overall health and well-being.
- Report any adverse events to the consultant, where appropriate.
- Ensure compatibility with any other medication initiated in primary care.
- Adjust the dose as advised by the specialist.
- Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
- Report adverse events to the MHRA (via Yellow Card) https://www.gov.uk/report-problem-medicine-medical-device

Clinical Particulars

BNF therapeutic class	**Tetracycline**
Cautions and Contraindications	**Contraindications** The use of demeclocycline is contraindicated in patients with acute porphyria, patients who are pregnant or breast-feeding, children under 12 years of age, patients with a history of hypersensitivity to tetracyclines and patients with renal impairment. **Special warnings and precautions for use** Demeclocycline should be used with caution in patients with renal or hepatic dysfunction, or in conjunction with other potentially hepatotoxic or nephrotoxic drugs. The treatment of chronic hyponatraemia may necessitate the administration of high doses of demeclocycline for prolonged periods, so increasing the potential for nephrotoxicity (manifested by rises in plasma urea and creatinine) and photoallergic reactions. Lower doses are indicated in cases of renal impairment to avoid excessive systemic accumulation and if therapy is prolonged, serum level determinations are advisable. Patients who have known liver disease should not receive more than 1g daily. In long term therapy, periodic laboratory evaluation of organ systems, including haematopoietic, renal and hepatic studies should be performed. Demeclocycline has the greatest potential of the tetracycline analogues for causing photo-allergic reactions in hypersensitive persons. Patients should be advised to avoid direct exposure of the skin to natural or artificial sunlight**.** Exacerbation of pre-existing SLE has been reported with tetracyclines. Patients taking oral contraceptives should be warned that if diarrhoea or breakthrough bleeding occur there is a possibility of contraceptive failure. Demeclocycline may increase muscle weakness in patients with myasthenia gravis.
Adverse Drug Reactions	**Undesirable effects** Gastrointestinal disturbances including nausea, vomiting, diarrhoea and rarely dysphagia have been reported. There have been a few cases of oesophagitis and oesphageal ulceration in patients taking oral tetracyclines in solid dose form, usually where medication was taken immediately before retiring or with inadequate fluids. In common with other tetracyclines, transient increases in liver function test values, hepatitis, jaundice and hepatic failure have been reported rarely. A few cases of pancreatitis have been reported. The most commonly reported dermatological reaction is photosensitivity.

	Erythematous, and maculo-papular rashes, pruritus, bullous dermatoses, exfoliative dermatitis and skin discolouration have occurred occasionally but serious skin reactions are rare. Headache, dizziness, visual disturbances and rarely impaired hearing have been reported with tetracyclines. Bulging fontanelles in infants and benign intracranial hypertension in juveniles and adults have been reported. Treatment should cease if evidence of raised intracranial pressure, such as severe or persistant headache or blurred vision are noted. While the condition and related symptoms usually resolve soon after discontinuation of the tetracycline, the possibility of permanent sequelae exists. There have been isolated cases of myasthenia. Hypersensitivity reactions including urticaria, Stevens-Johnson syndrome, angioneurotic oedema, anaphylaxis, anaphylactoid purpura, pericarditis and exacerbation of systemic lupus erythmatosus may occur. Renal dysfunction, especially in patients with pre-existing renal impairment, and rarely, acute renal failure or nephritis, have been reported with tetracyclines. Reversible nephrogenic diabetes insipidus can occur especially if treatment is prolonged and/or at high dosages. Haemolytic anaemia, thrombocytopenia, neutropenia, agranulocytosis, aplastic anaemia and eosinophilia have been reported rarely. When given over prolonged periods, tetracyclines have been reported to produce brown-black discoloration of the thyroid gland. No abnormalities of thyroid function are known to occur. **Effects on ability to drive and use machines** Headache, dizziness, visual disturbances and rarely impaired hearing have been reported with tetracyclines and patients should be warned about the possible hazards of driving or operating machinery during treatment.
Monitoring	See responsibilities of the specialist initiating treatment
Interactions	**Interaction with other medicinal products and other forms of interaction** ***Consult the BNF (https://www.medicinescomplete.com/#/) and SPC (https://www.medicines.org.uk/emc/) for a full list of interactions.*** The SPC states that demeclocycline should not be used with **penicillins.**[2] (Stockley's drug interactions[5] suggests that this interaction is important when treating serious infections such as pneumococcal meningitis and scarlet fever, where demeclocycline can reduce the effectiveness of penicillins. It is uncertain whether a similar interaction occurs in other infections). An interaction between demeclocycline and flucloxacillin is listed in the BNF since both demeclocycline and flucloxacillin can increase the risk of hepatotoxicity.[3] This interaction has not been assigned a severity but the

	combination should be used with caution. Tetracyclines depress plasma prothrombin activity and reduced doses of concomitant anti-coagulants such as **Coumarins** and **phenindione** may be required. Absorption of demeclocycline is impaired by the concomitant administration of milk and dairy products, food, **iron**, **calcium**, **zinc**, **magnesium** and particularly **aluminium** salts commonly used as antacids. Absorption of tetracyclines is possibly reduced by **kaolin**, **quinapril** tablets (quinapril tablets contain magnesium carbonate), **strontium ranelate**, **sucralfate**, **tripotassium dicitratobismuthate**. The concomitant use of tetracyclines may reduce the efficacy of **oral contraceptives**; an increased incidence of breakthrough bleeding may also be experienced (see section on special warnings and precautions for use). There is a possible increased risk of benign intracranial hypertension with concomitant use of tetracyclines and retinoids, e.g. **acitretin**, **isotretinoin**, **tretinoin**. There is increased risk of ergotism when tetracyclines given with **ergotamine** and **methysergide.** **Typhoid Vaccine (oral)**: Antibacterials inactivate oral typhoid vaccine and therefore demeclocycline should be avoided for 3 days before and after oral typhoid vaccine.

Communication

Specialist to GP
The specialist will inform the GP when they have initiated Demeclocycline. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking shared care. (Appendix A)

GP to specialist
If the GP has concerns over the prescribing of Demeclocycline, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	Telephone number	Email
Professor Hugh Jones, Consultant Physician & Endocrinologist	01226 431896	hugh.jones@nhs.net
Dr E Uchegbu Consultant Diabetologist	01226 432598	Elizabeth.uchegbu@nhs.net
Dr Z Merza Consultant Endocrinologist and Diabetologist	01226 435366	z.merza@nhs.net
Gillian Turrell, Lead Pharmacist Medicines Information / Cardiology, BHNFT	01226 432857	gilliansmith2@nhs.net

References

1. *Clinical practice guideline on diagnosis and treatment of hyponatraemia*, developed by a collaboration between the European Society of Intensive Care Medicine, the European Society of Endocrinology and the European Renal Association-European Dialysis and Transplant Association represented by European Renal Association. http://www.eje-online.org/content/170/3/G1.full Accessed <30/12/2020>
2. SPC. Ledermycin Capsules 150mg. Jan 2019. Available at: https://www.medicines.org.uk/emc/product/499/smpc Accessed <30/12/2020>
3. BNF. Available at: www.medicinescomplete.com Accessed <30/12/20>
4. Prescribing information for Demeclocycline for the treatment of chronic hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). NHS Telford and Wrekin CCG Medicines Management. November 2016. Available at: https://www.telfordccg.nhs.uk/your-health/medicines-management/shared-care-agreements-prescribing-information-documents/prescribing-information-documents/1386-demeclocycline-siadh-prescribing-information-nov-16/file Accessed <30/12/2020>
5. Stockley's Drug Interactions. https://www.medicinescomplete.com/mc/ Accessed <28/1/21>

Development Process

This guideline was developed following an AMBER classification status of demeclocycline hydrochloride for the treatment of chronic hyponatraemia associated with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the endocrinologists in Barnsley and was ratified at the Area Prescribing Committee on 9th June 2021.

Appendix A – Shared Care request form (Amber)

- Specialist to complete when requesting GP to enter a shared care arrangement.
- GP to return signed copy of form.
- Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**GP**): _____

Patient details

Name: _____ ID Number: _____

Address: _____ DOB: _____

Diagnosed condition: _____

Amber Drug details

Drug name: _____ Dose and frequency: _____

Date of initiation: _____ Length of treatment: _____

The patient will be reviewed by the Consultant on: _____

The patient should be reviewed by the GP by: _____

Monitoring

The following monitoring should be undertaken by the GP:

Parameter	Date next test due	Frequency

Communication

Consultant
Telephone number: _____ Fax number:_____

Email address: _____

Specialist Nurse
Telephone number: _____ Fax number: _____

Email address: _____

Confirmation of acceptance of shared care

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, Dr ……., can confirm I :

☐ accept the request to participate in shared care for the patient named above.

☐ reject the request to participate in shared care for the patient named above. The reason for this being ……..

GP signature: _____ Date: _____

To save resources you have been sent appendix A of the shared care document. The full document (*Demeclocycline Shared Care Guideline, date approved June 2021*) can be accessed on the Barnsley BEST website at the following link:
http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/
Or via the Barnsley Area Formulary: www.barnsleyformulary.nhs.uk