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A MONTHLY MEDICINES AND PRESCRIBING BULLETIN FOR HEALTHCARE PROFESSIONALS IN EAST LANCASHIRE FOCUSING ON NEW THERAPIES.

Monitoring Amiodarone Therapy

A recent INTERFACE article highlighted the adverse reactions of amiodarone, affecting the lungs, thyroid, liver, heart, eyes and nervous system. Although amiodarone is initiated by hospital specialists it is routinely prescribed in primary care, and as toxicities are numerous it is important to ensure that routine patient monitoring is carried out. The purpose of this article is to guide monitoring and review drug interactions.

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Baseline assessments undertaken by the hospital would normally include clinical examination, thyroid function tests (TFTs), liver function tests (LFTs), serum potassium, chest X-ray and an ECG.[1,2]

Some GP practice clinical systems now prompt practices to carry out 6 monthly TFTs (e.g. The EMIS system does this through 'Clinical Utilities'). Whilst checking TFTs this could provide the opportunity to carry out the other monitoring as detailed below.

The following tests should be undertaken in primary care on a regular basis or when indicated by potential side effects or worsening symptoms, and for several months after discontinuation of treatment.

Test required	Frequency	Action required if abnormal
TFTs Request TSH and state that the patient is on amiodarone. The lab will report T3 and T4 if necessary, depending on the TSH level	6 monthly[1,2]	**Hyperthyroidism** - Urgent referral to endocrinologist by fax or telephone, amiodarone will usually be stopped.[1] Liaise with cardiologist. **Hypothyroidism** - Liaise with cardiologist.
LFTs	6 monthly[1,2]	Isolated moderate increases in serum transaminases (1.5 to 3 times the upper limit of normal) occur commonly at the beginning of treatment which may return to normal with dose reduction or even spontaneously.[1] Amiodarone should be discontinued if liver enzymes are persistent high or severe (more than 3 times higher than normal), or clinical signs of liver disease develop and should be referred to gastroenterologist.[2]
U&Es	Regularly (If on diuretics 6 monthly)[2]	Correct hypokalaemia and monitor QT interval.[1] Liaise with cardiologist as necessary.
Opthalmological exam	The SPC recommends an annual ophthalmologic exam, although usually only recommended if visual disturbances occur.[1,2]	Corneal microdeposits are visible on slit-lamp examination in nearly all patients within the first month of starting amiodarone and are generally considered to be benign.[2] Discontinuation is seldom necessary unless the patient develops visual symptoms such as haloes or blurred vision. Optic neuritis, sometimes progressing to total blindness, appears to be very rare.[2] Ophthalmologic examinations (including fundoscopy) are needed if blurred or decreased vision occurs;

Monitoring of side effects may be picked up during medication review (6 monthly is suggested) or reported by the patient. They may present after the patient has stopped taking amiodarone, due to its long half life.

Unwanted effects	Action required
Pulmonary toxicity - suspect if new or increasing shortness of breath, unexplained cough or crackles develop.	Arrange urgent chest X-ray indicating the clinical concern to the radiologist. If the X-ray is compatible with amiodarone toxicity make an urgent referral to the respiratory department.[3]
Cardiac symptoms that develop or worsen	Refer back to cardiologist.
Visual symptoms e.g. haloes, blurred or decreased vision.	Refer to ophthalmology.
Peripheral neuropathy and / or myopathy	Urgent referral to neurologist and inform cardiologist.
Skin toxicity - photosensitive or non-photosensitive rash or blue-grey skin discolouration.	Advise patient to reduce exposure to sun and cover up / use high factor sunscreen. Skin discolouration slowly reverses once drug is stopped.

Amiodarone interacts with many drugs. See BNF appendix 1 for full listing. Drugs that can be predicted to interact include those that are metabolised by the cytochrome P450 enzymes of the liver, and drugs that prolong the QT interval. Some of the more important ones are detailed below. There is the potential for drug interactions to occur several weeks or months after amiodarone has been stopped.

Interaction	Action
Drugs that induce the cytochrome P450 enzymes of the liver e.g. carbamazepine, phenytoin, rifampicin.	Amiodarone levels will be lowered.
Drugs that inhibit cytochrome P450 enzymes e.g. cimetidine, grapefruit juice.	Amiodarone levels will be increased.
Amiodarone inhibits cytochrome P450 enzymes. Examples of other drugs that are metabolised by these enzymes include ciclosporin, phenytoin, verapamil, warfarin, simvastatin.	The dose of the interacting drug might need to be reduced. Also check for side effects of the interacting drugs - as the plasma concentration will be increased.
Drugs that prolong the QT interval e.g. other antiarrhythmic drugs such as disopyramide and sotalol; some antipsychotics, quinolone antibiotics, some macrolides, lithium and tricyclic antidepressants, antimalarials eg chloroquine, mefloquine.	Amiodarone also prolongs the QT interval and the combination should be avoided because of the risk of additive effects, which may lead to life-threatening torsades de pointes cardiac arrhythmia.[4]
Digoxin	Increase in plasma digoxin concentration. Halve digoxin dose. Monitor for signs of digoxin toxicity, review ECG and digoxin levels.[1]
Diuretics, systemic corticosteroids, and other drugs that cause hypokalaemia.	Monitor potassium levels. Hypokalaemia during amiodarone therapy may lead to life-threatening torsades de pointes cardiac arrhythmia.

References:
1. Sanofi-Aventis. Summary of Product Characteristics – Cordarone X 100/200 tablets. Last revision of text: July 2007.
2. Drug & Therapeutics Bulletin. Using amiodarone safely. Vol 41, No. 2, pages 9-12. Feb 2003.
3. Personal Communication (Email). Dr Green, Consultant Physician & Clinical Lead - Respiratory, East Lancashire Hospitals NHS Trust. 17th Dec 2007.
4. Baxter K. Stockley's Drug Interactions. 8th Edition, 2007. London, Pharmaceutical Press.

Medicines Management Board Guidance

Please see the MMB website for prescribing information on the following; www.elmmb.nhs.uk

RED LIST

Forceval capsules® -
Prevention of refeeding syndrome.

The NICE guidance **"Nutritional support in Adults, Clinical guidelines 32 (2006)"** recommends that patients at risk of refeeding syndrome should be given a multivitamin & micronutrient supplement, in addition to electrolyte replacement and gradual introduction of a full feeding regime. Forceval® is recommended for the prevention and management of refeeding syndrome only. Currently Forceval is the only preparation on the market which can provide a complete vitamin and micronutrient supplement. All prescribing is to be maintained by secondary care.

AMBER LIST

Rufinamide▼ (Inovelon®) –
Lennox-Gastaut Epilepsy.

Rufinamide should only be initiated or recommended by a specialist in the management of Lennox-Gastaut Syndrome (LGS) and other forms of epilepsy, after which prescribing may be passed to the primary care prescriber. Adequate advice on dose titration should be provided in every case. It should be used as a fourth line adjunctive therapy, usually in a combination with one or more of the following medicines; sodium valproate (unlicensed), topiramate or lamotrigine. Women of child-bearing potential taking rufinamide should be advised to use two forms of safe and effective contraception. Hypersensitivity syndrome – Serious hypersensitivity syndrome has developed especially in children and upon initiation of therapy; consider withdrawal if rash or signs or symptoms of hypersensitivity syndrome develop. Warn patients to seek immediate medical attention if signs or symptoms of hypersensitivity develop. The full review can be accessed online at www.elmmb.nhs.uk/new-drugs

BLACK LIST

Beclometasone/Formoterol▼ MDI Inhaler (Fostair®) – Asthma in adults.

Fostair® is not currently recommended for the management of asthma in adults. The lack of ability to use a spacer with this device, coupled with the lack of dose titration above the equivalent of 1000mcg beclometasone/day, coupled with other issues detailed in the new drug review do not support the use of this product at this time. This decision will be reviewed as more data on the use of this product is released. Not included in the East Lancashire Joint Formulary, and not stocked within secondary care. The full review can be accessed online at www.elmmb.nhs.uk/new-drugs

Retapamulin▼ cream (Altargo®) –
Topical infections.

Retapamulin is not currently recommended for the management of topical infections. In line with national guidelines, the judicious use of all anti-microbials is recommended. The lack of comparative efficacy with a range of usual treatments, a higher cost, and without support nationally through the Health Protection Agencies guidelines on the management of infections in primary care, this product cannot be supported. Not included in the East Lancashire Joint Formulary, and not stocked within secondary care. The full review can be accessed online at www.elmmb.nhs.uk/new-drugs

TRAFFIC LIGHT DEFINITIONS - See website for more information on these recommendations.

RED – Secondary care only (+/- recommendations)
AMBER – Secondary care initiates/recommends, then passes to primary care (+/- recommendations)
BLACK – Non-Formulary. Not recommended for prescribing in primary or secondary care

BLACK LIST continued...

Glucosamine/Chondroitin Supplements
(Various Brands) – Osteoarthritis.

The use of glucosamine or chondroitin products on NHS prescription is not recommended by NICE for the treatment of osteoarthritis. Evidence to support the efficacy of glucosamine hydrochloride as a symptom modifier is poor. For the non-licensed product (glucosamine sulfate), the evidence is not strong enough to warrant recommending that it should be prescribed on the NHS. One glucosamine hydrochloride product is licensed, it would not be cost effective to prescribe glucosamine on the NHS. Many people with osteoarthritis take over-the-counter nutriceutical products and may benefit from clear, evidence-based information. In particular, it was felt that it would be beneficial to advise people who wanted to trial over-the-counter glucosamine that the only potential benefits identified in early research are purely related to a reduction of pain (to some people, and to only mild or modest degree) with glucosamine sulfate 1500 mg daily. They could also benefit from advice on how to perform their own trial of therapy, that is, to evaluate their pain before starting glucosamine and ensure they review the benefits of glucosamine after three months. The full review can be accessed online at www.elmmb.nhs.uk/new-drugs

Melatonin▼ SR tablets (Circadin®) –
Primary insomnia in adults >55yrs.

Circadin® is not currently recommended for the management of primary insomnia in adults over 55yrs. The effects on quality of sleep and daytime functioning are minimal at best, and likely in a small proportion of patients only. It has not demonstrated benefits following an initial 3 week course, nor is there any published cost-effectiveness evidence to support its use. The lack of definitive date on the effects on some psychomotor or cognitive functions (e.g. driving), performance or withdrawal is also noted. Not included in the East Lancashire Joint Formulary, and not stocked within secondary care. The full review can be accessed online at www.elmmb.nhs.uk/new-drugs

Salmeterol/fluticasone 50/500 microgram Accuhaler (Seretide 500 Accuhaler®) is only recommended for use in COPD in line with current NICE guidance. NICE currently states that Seretide 50/500 Accuhaler® or Symbicort® can be used for patients who have an FEV1 less than or equal to 50% predicted, who are having two or more exacerbations requiring treatment with an antibiotics or oral corticosteroids in a 12 month period.

In line with the Scottish Medicines Consortium (SMC) guidance, Seretide50/500 Accuhaler® is not recommended for use for the symptomatic treatment of patients with COPD with a FEV1 50% to <60% predicted normal (pre-bronchodilator) and a history of repeated exacerbations, who have significant symptoms despite regular bronchodilator therapy. In this group, while there was an improvement in lung function tests and a reduction in both moderate and severe exacerbations with salmeterol/fluticasone in comparison with placebo, there was no difference in mortality rate over 3 years. In addition, a sufficiently robust economic case was not put forward to gain acceptance.

Comments and feedback

Contact Medicines Information on 01254 732 254 (based at BGH) or email Interface@bwdpct.nhs.uk.

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Query CORNER

What is the antidepressant of choice for patients with ischaemic heart disease?

Many antidepressant medicines are associated with adverse cardiovascular effects and we are often asked which agent would be considered most appropriate for patients with existing ischaemic heart disease (IHD). A 'Medicines Q&A' article has been published that addresses this question and considers the evidence.[1]

The majority of the relevant data available relates to tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). SSRIs are the antidepressants of choice in most patients.[2] Although there are limited data on their use in patients with IHD, SSRIs have not been found to have an adverse cardiovascular effect profile.

Sertraline is considered the SSRI of choice in patients with IHD and is recommended first line by NICE guidance in those patients with a recent myocardial infarction (MI) or unstable angina.

TCAs are known to cause adverse cardiovascular effects such as orthostatic hypotension, tachycardia and ECG changes. They should be used only with caution in patients with IHD and are contraindicated in patients who have had a recent MI.

1. www.nelm.nhs.uk/en/NeLM-Area/Evidence/Medicines-Q--A/What-is-the-antidepressant-of-choice-in-ischaemic-heart-disease/
2. www.nice.org.uk/guidance/index.jsp?action=byID&o=10958

ACEIs first line in preference to ARBs

The Prescription Pricing Division has published data for the prescribing of renin-angiotensin-system drugs. Angiotensin II receptor antagonists ('ARBs) account for 28% of prescriptions but 65% of the costs for this class of drugs. The report explains that ACEIs should be always be prescribed in preference to ARBs. Only where patients experience intolerable cough should the ACEI be substituted with an ARB. The ACEI which are favoured for use are ramipril and lisinopril.
www.ppa.org.uk/news/pact-042008.htm

Academic detail aids and supporting documents to promote best practice in prescribing renin-angiotensin-system drugs have been produced by the North West Medicines Information Centre in conjunction with PCT pharmacists in the North West and are freely available at
www.mmnetwork.nhs.uk/med-man-acaddetail.php

Asthma guidance

New guidelines for the management of asthma have been published by the British Thoracic Society (BTS) and Scottish Intercollegiate Guidelines Network (SIGN).
www.sign.ac.uk/pdf/sign101.pdf (128 pages)

An In Focus news article summarises the key changes from previous guidelines.
www.nelm.nhs.uk/en/NeLM-Area/News/494427/494566/494578/?query=bts+asthma&rank=3

Drug monitoring document

An updated guide to drug monitoring in primary care has been published on the National electronic Library for Medicines. At 36 pages, it is a comprehensive resource and suggests which tests are required and with what frequency for patients receiving medicines in primary care. www.nelm.nhs.uk (Click on 'Evidence Based Resources' in the list on the left hand side, then 'Drug Monitoring'.)

Product discontinuations

Mexitil (mexiletine) injection and **capsules** have been discontinued at the end of June 2008. Other agents remain available for the management of ventricular arrhythmias.

SPC Changes

Daktarin® (miconazole) oral gel is licensed for use in children from four months of age. It was previously licensed for infants from 28 days of age but the minimum age has been increased to reflect the risk of choking. In pre-term infants or those exhibiting low neuromuscular development, the manufacturers recommend the lower age limit should be increased by one or two months.

Neupro (rotigotine) transdermal patches must now be stored in the fridge. This is to reduce the incidence of crystallisation of the active substance in the patch. For further details, see:
www.nelm.nhs.uk/en/NeLM-Area/News/494717/494759/494769/