Oxford Radcliffe Hospitals NHS Trust and Oxfordshire Primary Care Trusts Shared Care Protocol and Information for GPs

AMIODARONE

This leaflet provides the necessary information and guidance for the shared care of adult patients requiring amiodarone therapy

Introduction
Amiodarone is an effective, but toxic, antiarrhythmic drug used in the management of both ventricular and atrial arrhythmias. It should only be initiated by, or under the direction of, a hospital consultant.

Indications
Amiodarone is used to prevent atrial fibrillation (AF), i.e. in patients who have paroxysmal AF or patients with persistent AF who are due to undergo DC cardioversion to restore sinus rhythm. It may also be continued after cardioversion to prevent AF recurrence in selected patients, although rarely long term. There is no role for Amiodarone in the treatment of permanent AF (i.e. it is not a rate-controlling drug for people in who there is no attempt to restore sinus rhythm). It is a second line drug, sometimes tried after Flecainide and/or Sotalol has failed. It may be first line in patients with AF who have heart failure.
The other group of patients who receive Amiodarone are those with structural heart disease at risk of ventricular tachycardia or ventricular fibrillation. The vast majority will have implantable cardioverter defibrillators (ICDs). The role of Amiodarone is to reduce the likelihood of needing a shock from their ICD.

Dose and administration
- Amiodarone has a very long half life (average of 58 days) and many weeks may be required to achieve steady-state plasma concentration; this is particularly important when drug interactions are likely (see later).
- Various loading regimes are quoted in the literature and up to three days may be required to achieve a therapeutic effect after oral administration. Large initial doses (loading doses) are required which are then followed by lower maintenance doses.
- The ORH currently recommends two oral loading regimens, termed the conventional and accelerated loading regimes.
- The conventional (licensed) loading regime is 200mg three times a day for one week, followed by 200mg twice a day for one week then a maintenance dose of 200mg or less daily; this is the oral regime of choice.
- The accelerated regime of 400mg three times daily for one week followed by a maintenance dose of 200mg daily is an unlicensed regime recommended only for the treatment of life-threatening ventricular arrhythmias.

- Onset of therapeutic effect with the intravenous formulation occurs in less than 30 minutes. The recommended intravenous loading regime at the ORH is 300mg over one hour followed by an infusion of 900mg over the following 24 hours. Patients should only be given intravenous amiodarone in hospital.

Preparations available
- 100mg and 200mg tablets
- 30mg/ml and 50mg/ml injections.

Adverse effects
- Amiodarone can cause a number of adverse reactions including effects on the eyes, heart, lung, liver, thyroid gland, skin and peripheral nervous system; see the Summary of Product Characteristics (SPC) for full details.
- These reactions are most often related to the total amiodarone exposure and are a result of drug accumulation in the tissues. Side effects slowly disappear as tissue levels fall.
- Following drug withdrawal, residual tissue-bound amiodarone may protect the patient for up to a month. However, the likelihood of recurrence of arrhythmia during this period should be considered.

Adverse effects to look out for include:
- hypo- and hyperthyroidism
- cirrhosis, hepatitis and jaundice
- reversible corneal microdeposits (sometimes with night glare)
- rarely impaired vision due to optic neuritis
- peripheral neuropathy and myopathy (usually reversible on withdrawal)
- bradycardia and conduction disturbances
- phototoxicity and rarely persistent slate-grey skin discolouration
- pulmonary toxicity (including pneumonitis and fibrosis)
- tremor
- sleep disorders

Contra-indications
- sinus bradycardia
- sino-atrial heart block
- unless a pacemaker is fitted, avoid in severe conduction disturbances or sinus node disease
- evidence or history of thyroid dysfunction
- hypersensitivity to iodine, amiodarone or any of the excipients
- pregnancy – see below
- lactation – see below

Pregnancy and lactation
- There are insufficient data on the use of amiodarone during pregnancy in humans to judge any possible toxicity. However, in view of its effect on the foetal thyroid gland, amiodarone is contraindicated during pregnancy, except in exceptional circumstances (see SPC or BNF).
- If, because of the long half life of amiodarone, discontinuation of the drug is considered prior to planned conception, the real risk of reoccurrence of life threatening arrhythmias should be weighed against the possible hazard for the foetus.

- Amiodarone is excreted into the breast milk in significant quantities and breast-feeding is contra-indicated.

Drug interactions (refer also to BNF or SPC)
Some of the more important drugs that interact with amiodarone include:
- warfarin - amiodarone raises the plasma concentrations of oral anticoagulants. The dose of warfarin should be reduced accordingly and more frequent monitoring of prothrombin time both during and after amiodarone treatment is recommended. Use INR to guide dose reduction.
- digoxin - administration of amiodarone to a patient already receiving digoxin will cause an increase in the plasma digoxin concentration. Reduce dose of digoxin by one third to one half.
- simvastatin – amiodarone inhibits CYP3A4 and there is some evidence of an increased incidence of myopathy when amiodarone is given with high doses of simvastatin; rhabdomyolysis has been reported in patients on the combination. Reduce dose of simvastatin to a maximum of 20mg daily unless the clinical benefit outweighs the risks.
- ciclosporin – reduce dose of ciclosporin and measure ciclosporin levels to guide dose reduction.
- flecainide – reduce dose of flecainide by one third to one half and monitor flecainide levels.
- phenytoin – amiodarone raises the plasma concentrations of phenytoin. Reduce dose of phenytoin if signs of overdosage appear and measure phenytoin levels to guide dose reduction.
- combined therapy with the following drugs which prolong the QT interval is contra-indicated due to the increased risk of torsades de pointes:
  - class Ia anti-arrhythmic drugs e.g. quinidine, procainamide, disopyramide
  - class III anti-arrhythmic drugs e.g. sotalol, bretylium
  - intravenous erythromycin, co-trimoxazole or pentamidine injection
  - some anti-psychotics e.g. chlorpromazine, thioridazine, fluphenazine, pimozide, haloperidol, amisulpiride and sertindole
  - lithium and tricyclic anti-depressants e.g. doxepin, maprotiline, amitriptyline
  - certain antihistamines e.g. terfenadine, astemizole, mizolastine
  - anti-malarials e.g. quinine, mefloquine, chloroquine, halofantrine.
- combined therapy with the following drugs is not recommended:

- beta blockers and certain calcium channel inhibitors (diltiazem, verapamil); potentiation of negative chronotropic properties and conduction slowing effects may occur
- stimulant laxatives, which may cause hypokalaemia thus increasing the risk of torsades de pointes.

Monitoring

- ECG monitoring is recommended after treatment has been established to assess the corrected QT interval. This will prolong however is unlikely to be harmful unless the QTc exceeds 500 ms.

- Liver function tests (LFTs) and thyroid function tests (TFTs) are required before starting treatment and then every six months. The initial testing is both to identify any problems which may be a caution or contra-indication to the use of amiodarone and as a baseline measurement against which the future results can be compared.

- The specific biochemical tests which are assessed at the ORH for LFTs are albumin, bilirubin, alanine transferase and alkaline phosphatase and all four of these tests should be performed.

- For TFTs, tri-iodothyronine (T3), thyroxine (T4) and thyroid-stimulating hormone (TSH) should all be measured (see BNF or SPC for full details).

- The lung fields should be auscultated every 6 months or if symptoms of cough, breathlessness or haemoptysis develop. Respiratory function tests and high-resolution CT may be required to investigate possible pulmonary fibrosis if the patient develops symptoms or auscultation reveals inspiratory crackles.

- Ophthalmological review is necessary if visual symptoms develop

Patient information leaflet

Patients should be supplied with an information leaflet from the manufacturer.

Shared Care Responsibilities

Shared care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them. Patients should be under regular follow-up which provides an opportunity to discuss drug therapy.

a) Hospital Consultant

- Carry out ECG monitoring, serum potassium measurements, LFTs and TFTs prior to treatment and communicate to patient's GP.
- Initiate treatment as per the ORH protocol and prescribe until the dose is stable (normally first 3 weeks) and/or the GP formally agrees to shared care.
- Write to the GP requesting shared care and outline shared care protocol criteria.
- Liaise with GP regarding changes in disease management, drug dose, missed clinic appointments.
- Ensure clinical supervision of the patient is done by follow-up as appropriate.
- Ensure the patient understands the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Be available to give advice to GP and patient.

b) GP

- Prescribe amiodarone once the dose is stable.
- Carry out ECG monitoring (where appropriate), serum potassium measurements, chest examination, LFTs and TFTs every six months and communicate to patient's consultant.
- Advise the hospital consultant of any clinical changes where appropriate.
- Monitor for adverse effects as detailed above.

c) Patient

- Report any adverse effects to their GP and/or consultant.
- Have regular monitoring as outlined above.