AMIODARONE

01. Assay details

CH Labs Test Reference Guide

02. Therapeutic range

1 - 2.5mg/L

How well established:
Although there is some evidence that plasma concentrations above 0.5 mg/L are required for antiarrhythmic effect, data showing a correlation between actual plasma concentration and antiarrhythmic activity is lacking. In a study of 127 patients, half of the patients with a plasma concentration < 1.0 mg/L had a recurrence of arrhythmia, comprising one third of all patients with a relapse. It has therefore been recommended that amiodarone concentrations are kept above 1.0 mg/L in patients with either supraventricular or ventricular arrhythmias.

Similarly, while serious toxicity is more likely at concentrations greater than 2.5 mg/L, its incidence is more reliably correlated with total drug use suggesting the importance of accumulation in target tissue over time. Amiodarone and its active metabolite desethylamiodarone, are found in much higher concentrations in tissues than in plasma. When amiodarone maintenance doses were titrated to achieve plasma concentrations < 2.5 mg/L, there was a relatively low incidence of side effects (25%). However, there is a considerable overlap of plasma concentrations in patients with and without side-effects, making it difficult to define a safe maximum plasma concentration of amiodarone.

03. Pharmacokinetics

F: 0.4 (range; 0.2 - 0.86)	**Vd** (L/kg): 77 (20-150)	**Cl** (L/h/kg): 0.05 (0.02-0.12)	**t½:** 1300 hrs (55 days) (900-1600 hrs)
Fe: 0	**Elimination route:** Hepatic metabolism, biliary + faecal excretion		
CYP: 3A & 2C8 substrate, inhibits 1A2, 2C, 2D6 & 3A & p-glycoprotein			**Protein binding:** 0.96

F = Bioavailability, Vd = volume of distribution, Cl = clearance, t½ = terminal half-life of elimination, Fe = fraction excreted unchanged in the urine, CYP = cytochrome P450 enzyme/s

Other PK data:

- The Tmax is 2-10 hrs.
- The onset of action is at 3 days-3 weeks. The peak effect occurs 1 week to 5 months after starting therapy. The duration of effect after discontinuation of therapy is 7-50 days.
- The t1/2 after a single dose is 3-21 hours (rapid tissue distribution followed by a slow phase of elimination).

- Desethylamiodarone (DEA), the main metabolite, is pharmacologically active and may contribute to the antiarrhythmic effects of amiodarone. DEA reaches serum concentrations 60-80% of those of amiodarone after chronic therapy. The t1/2 of DEA is 30-90 days.
- Total elimination of amiodarone and DEA from the body can take 4-6 months or longer.

04. Indications

1. Atrial tachyarrhythmias
2. Ventricular arrhythmias

05. Loading dose

Atrial fibrillation: 600-1200 mg/day (1-2 weeks); 400-600 mg/day (1-3 weeks).
Ventricular fibrillation: 800-1600 mg/day (1-3 weeks); 600-800 mg/day (approx. 4 weeks).

06. Maintenance dose

Atrial fibrillation: 100-200 mg per day.
Ventricular fibrillation: 200-400 mg per day.

Recent retrospective analysis suggests that the efficacy of low dose oral amiodarone, 200 mg/day for atrial and ventricular arrhythmias, is similar to that of high dose amiodarone.

07. Notes on administration

Administer consistently with regards to meals.

08. When to monitor

Trough concentrations should be measured, preferably just before the next dose.
Amiodarone has a very long half-life and a new steady-state will not be reached for several weeks/months after a dose change.

09. Dose individualisation

The wide variability in oral bioavailability, distribution and rate of elimination means that dose requirements vary widely. As a general rule, amiodarone dosing should be titrated to clinical effect and patients should receive maintenance therapy with the lowest dose possible.

10. Adverse effects

>10%

CNS: ataxia, fatigue, malaise, dizziness, headache, insomnia, nightmares
CVS: hypotension (IV)

DERM: photosensitivity
EYES: corneal microdeposits (70%) GI: nausea, vomiting
NEURO/SKEL: tremor, paraesthesia (18-54%), muscle weakness
RESP: pulmonary fibrosis, interstitial pneumonitis, alveolitis

1-10%

CNS: fever, sleep disturbances
CVS: congestive heart failure, cardiac arrhythmias (atropine-resistant bradycardia, heart block, sinus arrest, paroxysmal ventricular tachycardia), myocardial depression, flushing, oedema, local phlebitis (IV form)
DERM: solar dermatitis, blue skin discolouration
ENDO: hypothyroidism, hyperthyroidism, decreased libido
EYES: visual disturbance
GI: constipation, anorexia, abdominal pain, abnormal salivation, abnormal taste/smell (oral form)
HAEM: coagulation abnormalities
LIVER: abnormal LFT's

<1%

CNS: pseudotumour cerebri
CVS: hypotension (PO), vasculitis, atrial fibrillation, prolonged Q-T interval, ventricular fibrillation, cardiogenic shock
DERM: rash, alopecia, Stevens-Johnson syndrome
ENDO: epididymitis, hyperglycaemia, hypertriglyceridaemia
EYES: optic neuritis, photophobia
HAEM: thrombocytopenia
LIVER: cirrhosis, severe hepatotoxicity (potentially fatal hepatitis), increased transaminases

11. Drug interactions

Drugs that may increase the amiodarone concentration

(via enzyme inhibition, predominantly CYP3A3/4)
Anastrozole, cimetidine, erythromycin, clarithromycin, dextropropoxyphene, diltiazem, verapamil, grapefruit juice, azole antifungals (ketoconazole, fluconazole, itraconazole), protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir), isoniazid, metronidazole, nefazodone, norfluoxetine (active metabolite of fluoxetine), pimozide, quinidine, valproate.

Drugs that may decrease the amiodarone concentration

(via enzyme induction, predominantly CYP3A3/4)
Phenytoin, rifampicin, carbamazepine, phenobarbitone, primidone, efavirenz, nevirapine, ethanol, dexamethasone, methylprednisolone, prednisolone and prednisone.

Cholestyramine may increase the enterohepatic elimination of amiodarone resulting in decreased serum concentrations and half-life.

Amiodarone can increase the concentration of the following drugs:

(predominantly by inhibition of CYP3A3/4, 2C9 or 2D6)

Warfarin (may need to decrease the dose by >50%), aprinidine, budesonide, clonazepam, ciclosporin, lignocaine, procainamide, propafenone, quinidine, digoxin (by P-glycoprotein inhibition, may need to reduce digoxin dose by 25-50%).

Amiodarone impairs methotrexate's metabolism resulting in methotrexate toxicity.

Amiodarone can theoretically increase the serum concentrations of: NSAIDs, anticonvulsants, most antidepressants and antipsychotics, other antiarrhythmics including beta-blockers and calcium channel antagonists, some benzodiazepines (clonazepam, diazepam, midazolam, triazolam), some non-sedating antihistamines (fexofenadine, loratadine), macrolide antibiotics, immunosuppressants, some cytotoxics (busulphan, cyclophosphamide, docetaxel, etoposide, paclitaxel, vincristine, vinblastine), protease inhibitors, statins and some steroids (betamethasone, dexamethasone, hydrocortisone, methylprednisolone, prednisone).

Pharmacodynamic interactions

- Concurrent use of calcium channel antagonists and beta-blockers can result in AV block or bradycardia, especially following restoration of sinus rhythm in patients with atrial fibrillation.
- Amiodarone prolongs the Q-T interval and inhibits the metabolism of other drugs that do the same eg. quinidine, lignocaine, flecainide, sotolol, TCAs, pimozide, cisapride, chloroquine, glibenclamide, mefloquine, salbutamol, theophylline. Coadministration of amiodarone with the following drugs that prolong the Q-T interval should also be avoided: dofetilide, disopyramide, gatifloxacin, grepafloxacin, halofantrine, ibutilide, levofloxacin, levomethadyl, mexiletine, moxifloxacin, sparfloxacin and lithium.
- Coadministration with fentanyl, ritonavir or sparfloxacin can increase the risk of amiodarone-induced cardiotoxicity.
- Pyridoxine should be avoided in patients with amiodarone-induced photosensitivity reactions, as pyridoxine can potentiate the photosensitivity.

12. Factors that may give a false assay result

Amiodarone and DEA are unstable and blood samples should be protected from light.

13. Overdose

TOXINZ

14. Dialysability

Not dialysable

15. Comments

The therapeutic range is based on reporting only the parent drug concentrations, even though the metabolite is active. Exclusion of the metabolite concentration (which may be higher than that of the parent molecule) may be a factor in the failure to define a clear therapeutic range.

16. Key references

1. Campbell TJ & Williams KM. Therapeutic drug monitoring: antiarrhythmic drugs. Br J Clin Pharmacol 1998; 46: 307-319
2. Maling T. Amiodarone therapeutic plasma concentration monitoring, is it practical? Clin Pharmacokinetics 1988; 14: 321-324
3. Gill J, Rennie C, Fitton A. Amiodarone an overview of its pharmacological properties and review of its therapeutic use in cardiac arrhythmias. Drugs 1992; 43(1): 69-110
4. Amiodarone in Drug Information Handbook 7th Edition 1999-2000. Lacy CF, Armstrong LL, Goldman MP, Lance LL

17. Date

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