Amiodarone

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Summary

Amiodarone is the most effective antiarrhythmic drug available. In most countries (including Australia), amiodarone is the most commonly prescribed antiarrhythmic apart from drugs such as digoxin and beta blockers. Amiodarone can be used to treat tachyarrhythmias, including atrial fibrillation, ventricular tachycardia and patients at high risk of sudden cardiac death. Although amiodarone is effective, it is not generally recommended for minor rhythm disturbances because of its toxicity. It is a difficult and challenging drug to use in clinical practice. This is because of its very prolonged half-life and because of its multiple adverse effects.

Key words: adverse effects, arrhythmia.

Introduction

Amiodarone is an antiarrhythmic drug with structural similarities to thyroxine. It exhibits all four of the classic Vaughan Williams mechanisms of action, namely sodium and potassium channel blockade, a mild antisympathetic action and some calcium channel blockade, but it is usually classified as a Class III antiarrhythmic drug (see Table 1). It prolongs the refractory period in all cardiac tissues.

After oral administration, amiodarone only has a bioavailability of 30%. It also has a half-life of approximately 50 days, so it can take weeks for therapeutic effects to appear.

While amiodarone has many pharmacological effects, it also has many adverse effects. As some of these adverse reactions are life-threatening, it is important only to prescribe amiodarone for indications where it has a significant benefit over other treatments.

Indications

Although amiodarone has many possible uses, its main indications are severe cases of tachyarrhythmia (see Box 1).

Atrial fibrillation

For acute reversion of recurrent episodes of atrial fibrillation, whether paroxysmal (reverting spontaneously within hours to days if left untreated) or persistent (generally requiring intervention to return the patient to sinus rhythm), amiodarone is approximately as effective as flecainide. Both drugs are significantly more effective than placebo. One advantage of amiodarone, despite its significantly slower onset of action, is that it slows the heart rate even if the heart does not revert to sinus rhythm, whereas flecainide does not normally slow the ventricular response to atrial fibrillation and has been known to accelerate it.

Sotalol is also commonly used for acute reversion of atrial fibrillation, but has not been convincingly shown to be any more effective than standard intravenous beta blockers or even placebo. Again, sotalol and other beta blockers do have the advantage of slowing the ventricular response even if reversion does not occur.

Three large randomised trials of chronic therapy for paroxysmal/persistent atrial fibrillation have convincingly shown amiodarone to be significantly superior to sotalol and

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Table 1

Simplified Vaughan Williams classification of antiarrhythmic drugs

Class	Action	Examples
I	Interfere with depolarisation	disopyramide quinidine mexiletine flecainide
II	Beta blockade	beta blockers other than sotalol
III	Prolong repolarisation	amiodarone sotalol
IV	Calcium channel blockade	verapamil

Box 1

Indications

- Recurrent (paroxysmal or persistent) atrial fibrillation or flutter.

- Patients at intermediate risk of arrhythmic death, especially post-myocardial infarction patients with moderate left ventricular dysfunction and patients with heart failure. Amiodarone is usually only given if significant or symptomatic ventricular arrhythmias are present.

- Patients with an implantable cardioverter-defibrillator whose quality of life is impaired by regular discharges of the defibrillator.

propafenone (a close relative of flecainide). Since sotalol has roughly equivalent efficacy to quinidine, and propafenone has very similar efficacy to flecainide, one can conclude that patients with recurrent atrial fibrillation given amiodarone are approximately twice as likely as those given one of the other drugs to be maintained in sinus rhythm 12 months after starting treatment.[1,2,3]

There is no point in using amiodarone in patients with established, permanent atrial fibrillation. There are safer drugs for achieving ventricular rate control, including beta blockers, diltiazem, verapamil and digoxin.

Ventricular tachyarrhythmias

Amiodarone is effective for minor ventricular arrhythmias such as ventricular ectopy and non-sustained ventricular tachycardia, both in patients with normal hearts and those with heart failure, coronary disease or hypertrophic cardiomyopathy. However, antiarrhythmic drugs are generally not recommended for these patients because of concern about possible aggravation of arrhythmia (so-called 'proarrhythmia'). Amiodarone should therefore be reserved for those at significant risk of life-threatening ventricular arrhythmias. These patients are subdivided into those at 'high' risk of fatal arrhythmia (survivors of life-threatening ventricular arrhythmia including ventricular fibrillation) and those at 'intermediate' risk (severe left ventricular dysfunction or non-sustained ventricular tachycardia).

High-risk patients

An early study of survivors of cardiac arrest in the era before implantable cardioverter-defibrillators became available, showed amiodarone to be superior to traditional antiarrhythmic drugs, such as quinidine and procainamide, in prolonging survival. More recent studies have compared implantable cardioverter-defibrillators with amiodarone in survivors of life-threatening ventricular arrhythmias.

Meta-analysis of three large studies showed clear superiority of implantable cardioverter-defibrillators over amiodarone overall.[4] However, when the patients in these studies were divided according to whether or not their left ventricular ejection fraction (EF) was moderately to severely impaired (defined as EF < 35%), it became apparent that the advantage of the defibrillators was largely confined to those patients with an EF < 35%.[4] Patients with a history of symptomatic ventricular tachyarrhythmias and normal left ventricular function had similar outcomes whether they were randomised to an implantable cardioverter-defibrillator or amiodarone.

Intermediate-risk patients

Patients at intermediate risk of arrhythmic death are those with left ventricular dysfunction and clinical heart failure, and those with additional risks such as low ejection fraction or non-sustained ventricular arrhythmias following a myocardial infarction. Meta-analysis of several large placebo-controlled trials in these patients suggests a 20–30% reduction in the risk of cardiac arrest or arrhythmic sudden death with amiodarone. This is statistically significant[5], however the reduction in overall mortality is of the order of 13% and is of borderline statistical significance. In view of the marginal efficacy in terms of total mortality, the serious adverse effects and the advent of implantable cardioverter-defibrillators, these studies (which did not include implantable cardioverter-defibrillators) have not led to the widespread use of amiodarone for patients of intermediate risk. In practice the decision is whether or not to implant a cardioverter-defibrillator.

More recently, a large randomised trial involving patients with severe left ventricular dysfunction (EF < 30%) has compared an implantable cardioverter-defibrillator with amiodarone and placebo. There was no difference in deaths from any cause between amiodarone and placebo at either three years or five years. Implantation of a cardioverter-defibrillator was associated with a clinically and statistically significant decrease in mortality at both time points.[6] Sub-group analysis also showed significant benefit for the implantable cardioverter-defibrillator in patients with underlying coronary artery disease, confirming the findings of the MADIT II study in post-myocardial infarction patients with ejection fractions less than 30%. The sub-group with normal coronary arteries (that is with dilated cardiomyopathy) showed a non-significant, but strong, trend in favour of treatment with an implantable cardioverter-defibrillator.[7]

Adjuvant therapy in patients with implantable cardioverter-defibrillators

A number of antiarrhythmic drugs, including amiodarone, have found a role in patients with implantable cardioverter-defibrillators which are functioning effectively but firing frequently and hence causing major reductions in quality of life. Antiarrhythmic drugs can reduce the frequency of shocks. The fear of lethal proarrhythmia associated with many of the drugs is lessened by the presence of the implantable cardioverter-defibrillator. A very recent comparative study reported combination therapy with amiodarone and a beta blocker to be markedly and significantly more effective at reducing implantable cardioverter-defibrillator shocks than either beta blocker alone or sotalol.

Administration and dosage (see Table 2)

Amiodarone can be given orally or intravenously. Intravenous administration is only appropriate in hospital with continuous ECG monitoring.

Intravenous dosing

Amiodarone can be given intravenously for supraventricular or ventricular arrhythmias, but should be reserved for urgent cases. Acute atrial fibrillation with a rapid ventricular response is

Table 2	
Dosing	
Intravenous (use central vein where possible)	300 mg over 20 min–2 hours
	900 mg infused over subsequent 24 hours (maximum 1200 mg in 24 hours)
	Then usually switch to oral maintenance dose if indicated
Oral	Loading dose of 200–400 mg three times a day for 10–14 days
	Maintenance of 200–400 mg/day thereafter (typically 200 mg/day and consider 100 mg/day for long-term treatment of atrial fibrillation)

not usually symptomatic enough to require intravenous therapy and often responds quite well to oral therapy with a range of drugs including amiodarone.

Life-threatening ventricular tachyarrhythmias are generally best treated with direct current cardioversion (definitely so if the patient is unconscious or markedly hypotensive). In some settings, however, particularly if the arrhythmia is recurrent despite direct current shocks, intravenous amiodarone can be very useful.

Intravenous amiodarone can cause acute hypotensive reactions and is often damaging to veins so it should normally be given through a central line. Dosage regimens vary, but a regimen commonly used in adults in Australia is 300 mg infused over a period of 20 minutes to two hours, followed by a further 900 mg over the next 24 hours (with continuous ECG and blood pressure monitoring). Unless the patient is unable to take amiodarone orally, it is unusual to continue intravenous therapy beyond 24 hours and a switch to oral therapy would normally be made at this time.

Oral dosing

Dosage regimens for oral amiodarone vary even more widely than the intravenous ones. While the drug will often be commenced in hospital, it is not unusual for oral amiodarone to be started in the community. Typical maintenance doses are approximately 200 mg daily and in non-urgent situations it may well be appropriate to start the patient on this dose. As amiodarone has an extremely long plasma half-life, it can take a long time to reach a therapeutic concentration and loading doses are therefore frequently used to accelerate this process.

When loading is desired, doses of 200–400 mg three times daily for 10–14 days may be used, followed by a reduction in one or two steps to a maintenance dose of 200–400 mg/day (usually 200 mg). It is very important to remember to reduce the dose. In some patients (for example the elderly), it is worth trying to reduce further to 100 mg/day after 2–3 months at 200 mg/day.

As a general rule, the doses used for life-threatening arrhythmias are higher than those for atrial fibrillation. Loading doses are sometimes associated with nausea, and this may limit their use.

There is some correlation between efficacy and the plasma concentration of amiodarone. There may be a little more correlation between adverse effects and plasma concentration, but adverse effects can occur within the therapeutic range. Routine measurement of plasma concentrations is not commonly performed.

Adverse effects

Nausea and vomiting are common and tend to occur early, particularly with loading doses. Many other adverse effects are chronic rather than acute and may appear months or even years after starting amiodarone. Constipation, anorexia, taste disturbance, benign corneal microdeposits, and blue-grey pigmentation of the skin which is slow to appear but generally irreversible, are all relatively common in chronic usage. Increased sensitivity to sunlight is often seen. Patients should be cautioned against exposure to the sun and warned that traditional 'UV blockout' lotions may not protect them, as some of the increased sensitivity is to visible light rather than ultra-violet light. If specifically asked, 10–20% of patients will report sleep disturbance with vivid dreams, although this often improves with time and/or a dose reduction. Some patients develop extrapyramidal symptoms or peripheral neuropathy.

Neurological complications occur, particularly in patients taking long-term amiodarone at relatively high doses (generally 300–400 mg/day). The commonest manifestation of this is a peripheral neuropathy which can be sensory and/or motor, with a glove and stocking distribution. This is not always reversed by stopping amiodarone, so treating physicians must be alert for the first signs of neuropathy.

A number of syndromes cause considerable concern in the medium to long term. These include chronic hepatitis, thyroid dysfunction and pulmonary toxicity (which can be acute and responsive to steroids, but more commonly is a chronic fibrotic form). There is no real evidence for the widely-held belief that patients with pre-existing chronic lung disease are more susceptible to pulmonary complications, although once again it is probably wise to be cautious and perhaps to monitor these patients more closely. If the indication for amiodarone is compelling, lung disease should not necessarily be an absolute contraindication.

Hypothyroidism is more common in iodine-replete regions of the world while thyrotoxicosis is seen more frequently in areas where iodine is relatively deficient in the diet. It is sometimes possible to continue amiodarone therapy and treat thyroid toxicity, but whenever possible the drug should be ceased if thyroid toxicity is detected. Amiodarone should also be stopped if hepatitis or lung disease are suspected or proven.

A major electrophysiological effect of amiodarone is prolonging the repolarisation of the cardiac action potential.

This automatically prolongs the QT interval on the ECG so QT prolongation, sometimes quite marked, is a feature of the therapeutic effect of amiodarone. For reasons which are not entirely clear, the much feared complication of torsades de pointes is much less commonly seen with amiodarone than with other drugs that prolong the QT interval. This is probably because amiodarone also blocks calcium channels. Anything that reduces intracellular calcium concentrations tends to make torsades de pointes less common in experimental models. However, patients are not protected if they have already experienced torsades de pointes with other QT-prolonging drugs. These patients should not be treated with amiodarone unless there is absolutely no alternative.

Amiodarone can cause atrio-ventricular block. The drug should be ceased, but if continued therapy is considered essential permanent pacing will probably be required.

As amiodarone is a 'Category C' drug it should not be used during pregnancy or lactation.

Drug interactions

There are a number of important drug interactions with amiodarone (see Box 2). Some of these interactions are related to the inhibition of cytochrome P450 3A4. The long half-life gives amiodarone the potential to cause interactions weeks after it has been ceased.

Amiodarone increases concentrations of digoxin (sometimes to a clinically significant degree) and impairs the metabolism of warfarin, tending to potentiate its anticoagulant effect. Similarly the concentrations and effects of flecainide, quinidine, phenytoin and cyclosporin tend to rise with amiodarone. These interactions and others need to be taken into account when patients taking these drugs start amiodarone. Similar considerations

apply to drugs such as atorvastatin and simvastatin which are metabolised in the liver by cytochrome P450 3A4. Amiodarone may impair their metabolism and hence potentially increase the risk of myopathy or rhabdomyolysis. The use of pravastatin as an alternative is probably to be preferred as it is not metabolised by cytochrome P450 3A4.

In the liver, amiodarone is metabolised to desethylamiodarone, which has similar activity and kinetics to the parent compound. This metabolism is almost completely inhibited by grapefruit juice, although it is not clear that this alters the clinical efficacy or toxicity in any significant way.

Amiodarone can cause bradyarrhythmias and this effect will be enhanced by co-administration with beta blockers, verapamil or diltiazem. There is some evidence of synergy between beta blockers and amiodarone in terms of efficacy against tachyarrhythmias and the combination is not necessarily contraindicated. It should simply be used with caution.

Baseline assessment and long-term monitoring

There are several guidelines for prescribing amiodarone. The most widely cited guideline is that of the North American Society of Pacing and Electrophysiology (recently renamed Heart Rhythm Society).[8] This recommends a number of baseline and follow-up tests (Table 3). It is clear, however, that these guidelines are variably applied by clinicians. A recent review suggested about 50% of the patients starting amiodarone received minimum baseline evaluation and less than 25% received the recommended ongoing surveillance.[9]

Baseline and intermittent (every 3–6 months) measurement of thyroid and liver function is certainly a sensible precaution. A high level of awareness is at least as important in detecting the often subtle changes of thyroid dysfunction in an ageing patient. Both interpretation of thyroid function tests and treatment of abnormalities, particularly hyperthyroidism, can be difficult in a patient taking amiodarone.[10]

Box 2

Drug interactions of amiodarone

Anaesthetics

Antiarrhythmic drugs
    disopyramide, flecainide, procainamide, quinidine

Cyclosporin

Digoxin

HMG CoA reductase inhibitors
    atorvastatin, simvastatin

Phenytoin

Protease inhibitors
    indinavir, ritonavir

Warfarin

Potential interactions with other drugs

■ metabolised by cytochrome P450 3A4

■ prolonging the QT interval

Table 3

Recommendations for monitoring of chronic dosing [8]

Test	Timing
Liver function tests	Baseline and every 6 months
Thyroid function tests	Baseline and every 6 months
Serum creatinine and electrolytes	Baseline and as indicated
Chest X-ray	Baseline and yearly
Ophthalmic evaluation	Baseline if visual impairment or for symptoms
Pulmonary function tests (including testing the diffusion capacity for carbon monoxide (DLCO))	Baseline and for unexplained symptoms or X-ray changes

Amiodarone-induced hepatic toxicity can manifest subtly as general malaise, anorexia, nausea or as classic hepatitis with right upper quadrant pain. Most frequently it is mild and essentially asymptomatic.

There is disagreement and a lack of evidence to guide monitoring for pulmonary toxicity. The Adverse Drug Reactions Advisory Committee has recently recommended that 'Lung function should be monitored including 6-monthly chest x-ray, and the development of dyspnoea or cough should be investigated immediately'.[11] This differs from the recommendations in Table 3, which include pulmonary function tests, including diffusion capacity, at baseline. The safest advice would be to follow the recommendations given in Table 3, but these are not currently widely practised in Australia. As there is no good evidence that any of these recommendations reduce the risk of life-threatening pulmonary complications, it is really left to the individual practitioner to decide what to do.

The development of a new cough or unexplained febrile syndrome during amiodarone therapy should certainly alert one to the possibility of pulmonary toxicity. Amiodarone should be ceased at once and formal pulmonary function testing undertaken.

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In 1997 Professor Campbell chaired the group which produced the 'Amiodarone Consensus Guidelines: use in Australasian clinincal practice' for Sanofi Winthrop.

Self-test questions

The following statements are either true or false (answers on page 159)

5. Amiodarone can cause hypothyroidism or hyperthyroidism.

6. Amiodarone can slow the heart rate of patients with atrial fibrillation even if they do not revert to sinus rhythm.

Wallchart

Copies of the wallchart 'Medical management of severe anaphylactoid and anaphylactic reactions' are still available from *Australian Prescriber*. This A3-sized chart was published as an insert to *Australian Prescriber* Vol 24 No. 5, 2001. It was endorsed by the Australasian College for Emergency Medicine, the Australasian Society of Clinical Immunology and Allergy, the Australian and New Zealand College of Anaesthetists, the Royal Australasian College of Physicians, the Royal Australian and New Zealand College of Radiologists, and the Royal Australian College of General Practitioners.

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