ARTICLE

Amiodarone in the aged

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SUMMARY

Amiodarone is a highly effective antiarrhythmic drug, but can have serious adverse effects, particularly in older patients. If possible it should not be used purely for controlling the heart rate.

If a prescription for amiodarone is contemplated, particularly for an older patient, consult a cardiologist. Avoid amiodarone in patients with significant conduction system disease, significant liver or pulmonary disease, or hyperthyroidism.

Regular monitoring of the patient, clinically and biochemically, is required to identify complications at an early, treatable stage. Maintain a high level of suspicion if a patient taking amiodarone is experiencing adverse reactions and presents with new symptoms.

Consider potential drug interactions when other drugs are prescribed with amiodarone. The effects and toxicities of amiodarone may persist weeks after it is stopped.

Introduction

Amiodarone is widely considered to be the most effective antiarrhythmic drug available.[1] It is commonly used to treat atrial fibrillation and ventricular arrhythmias. Amiodarone, and its active metabolite desethylamiodarone, have multiple effects on cardiac depolarisation and repolarisation. Although it primarily blocks potassium channels, amiodarone potentiates its effect through all four of the classic Vaughan Williams mechanisms of antiarrhythmic action.

Despite its efficacy, amiodarone is a challenging drug to use in clinical practice due to its prolonged half-life, multiple adverse effects and drug interactions. These adverse effects are particularly problematic for older people who are more susceptible to drug toxicities and who have higher rates of polypharmacy. There is also a lack of information regarding the safety of amiodarone in older people.[2] A cardiologist's opinion is recommended before prescribing.

Amiodarone can have adverse effects in multiple organ systems including the lungs, heart, liver, thyroid, gut, skin, nerves and eyes.[3] Its use is also implicated in a range of drug–drug interactions with commonly prescribed cardiovascular drugs.[4]

Indications

Amiodarone is one the most frequently prescribed antiarrhythmic drugs for atrial fibrillation.[5] It is used by 8–11% of patients.[6]

Atrial fibrillation is the commonest arrhythmia in older adults, with an estimated prevalence of 9% in people over the age of 80 years. The primary goals in management are to prevent disabling symptoms through rhythm or rate control and to reduce the risk of stroke with anticoagulation.[7]

Several major trials have compared rate and rhythm control in patients with atrial fibrillation. They found no significant difference in all-cause mortality, cardiovascular death and composite end points including death, stroke, major bleeding, cardiac arrest and congestive cardiac failure.[7] In fact, the AFFIRM study of over 4000 patients showed a trend towards increased mortality with rhythm control, particularly in older patients.[8] The differences were partly explained by non-cardiac deaths with antiarrhythmic therapy that was thought to be more toxic in those with serious medical conditions. There were no differences between the two groups in terms of cardiovascular mortality, deaths due to arrhythmia, vascular events or rates of ischaemic stroke.[9] The majority of the patients treated with rhythm control in AFFIRM were managed with amiodarone. Other, smaller studies have shown similar increases in non-cardiac mortality in patients taking amiodarone.[9,10]

Based on the trial results, rate control is preferred to rhythm control for patients with atrial fibrillation. Either beta blockers or non-dihydropyridine calcium channel blockers can be used.

The 2018 Australian Clinical Guidelines for the Diagnosis and Management of Atrial Fibrillation[11] state, 'Amiodarone should be considered a last-line option for chronic pharmacological rate control, given its toxicity profile.' Amiodarone may be considered for maintenance of sinus rhythm as a second-line drug,

or a first-line drug in the setting of left ventricular dysfunction, left ventricular hypertrophy or coronary artery disease. While no comment is made specifically about older patients in the guidelines, beta blockers should still be considered first-line drugs in this population.[11] For patients on long-term treatment, the indication for continuing amiodarone should be reviewed.

Intravenous amiodarone is indicated to terminate acute ventricular tachycardia in haemodynamically stable patients. It can also be used in the acute management of patients who become haemodynamically stable after maximal energy shock. Amiodarone can suppress events in patients with ischaemic heart disease and non-ischaemic cardiomyopathy who have recurrent ventricular arrhythmias.[12]

Pharmacokinetics and dosing

Amiodarone has incomplete and erratic absorption following oral administration. It is markedly lipophilic, resulting in a large volume of distribution (average approximately 66L/kg) and subsequently a long half-life.[4] Estimates of half-life vary, however a terminal half-life of up to 142 days has been reported as tissue stores deplete.[1] The principal active metabolite, desethylamiodarone, is reported to have a half-life of 60–90 days in chronic oral dosing.[13] Most of the drug is excreted via the liver and gastrointestinal tract by biliary excretion.

The plasma half-life and drug concentrations of amiodarone are further increased in older people due to an increased volume of distribution resulting from proportional increases in body fat. While the plasma concentration of amiodarone can be estimated, this is of limited value as the measurement is inaccurate and does not correlate well with efficacy or adverse effects.[1]

The typical maintenance dose of amiodarone is 200 mg per day. In older patients, decreasing the dose to 100 mg per day is advised, particularly if the indication is atrial fibrillation rather than a life-threatening arrhythmia.[4] The lowest effective loading and maintenance dose should be used in older patients and dose increases should be undertaken with caution. Unlike in ventricular arrhythmias, loading doses are often unnecessary for treating atrial fibrillation.

Given the long half-life, it may take weeks before dose increases yield clinically apparent effects, suggesting the need for cautious and slow up-titration. Similarly, clinicians should be aware that the effects and toxicities of amiodarone can still be present weeks to months after stopping the drug.

Drug interactions

Amiodarone inhibits cytochrome P450 (CYP) enzymes 3A and 2C and the drug transporter P-glycoprotein.[9] This leads to impaired metabolism and, potentially, increased sensitivity of patients to several drugs including warfarin, digoxin, non-steroidal anti-inflammatory drugs, statins and benzodiazepines.[14]

If amiodarone is added to warfarin, the warfarin dose must be reduced and INR should be closely monitored.[6] Interactions between amiodarone and the direct thrombin inhibitor dabigatran have been associated with a 50–200% increase in the area under the curve, resulting in a potentially increased risk of bleeding.[15] Similarly, non-randomised studies have reported a potential increase in the risk of bleeding with concurrent use of amiodarone and rivaroxaban,[16] although this interaction has not been described with apixaban and amiodarone.[17]

Amiodarone can also lead to bradyarrhythmias with an increased risk of complete heart block when used in combination with beta blockers or calcium channel blockers. Amiodarone commonly causes QT prolongation on the ECG and should be used with caution when combined with other drugs that also prolong the QT interval. However, induction of polymorphic ventricular tachycardia is uncommon.[1]

Grapefruit juice inhibits CYP3A4 leading to significantly reduced conversion of amiodarone to its active metabolite desethylamiodarone. Grapefruit juice should therefore be avoided with amiodarone therapy.[18]

Organ-specific complications

Older people are at an increased risk of the organ-specific complications of amiodarone. This is because of changes to pharmacokinetics as well as higher rates of medical comorbidities, physiological deterioration in renal and hepatic function, and higher rates of cognitive, motor and sensory impairment.[14] Older people may also present with non-specific complaints secondary to amiodarone including fatigue, nausea and anorexia. A high index of suspicion should be maintained if an older patient presents with new symptoms. Regular monitoring is recommended (see Table). The long half-life of amiodarone means that complications may emerge after the drug is ceased.

In a review of 1020 cases of reported amiodarone-induced toxicity, the most commonly reported adverse reactions were thyroid disorders, followed by skin reactions such as photosensitivity. Pulmonary toxicity was the third most common adverse event, but is considered the most serious as it is associated with increased mortality.[19]

Table **Monitoring for organ-specific complications of amiodarone**

Baseline assessments: Liver function, thyroid function, ECG, lung function, chest X-ray, review other drugs.

Organ	Complications	Symptoms	Suggested monitoring	Recommendation
Lungs	Acute inflammation, chronic fibrosis	Cough, increased breathlessness	Yearly chest X-ray Prompt assessment of new respiratory symptoms possibly with chest X-ray and pulmonary function tests	Stop amiodarone, start steroids Refer to respiratory physician
Heart	Bradycardia, heart block, QT prolongation	Dizziness, syncope, collapse, fatigue	Yearly ECG	Reduce dose
Liver	Hepatitis	Often asymptomatic Nausea, gastrointestinal disturbance	6–monthly liver function tests	Discontinue if transaminases >3 x normal Avoid in severe liver disease
Thyroid	Hypothyroidism 20% Hyperthyroidism 3%	Often asymptomatic Fatigue, palpitations, weight change	6–monthly thyroid function tests	Start thyroxine for hypothyroidism Discontinue in hyperthyroidism and consider antithyroid drugs, prednisone, or surgical thyroidectomy and refer to an endocrinologist
Skin	Photosensitivity		Physical examination at baseline, then as needed based on signs or symptoms	Stress importance of sunscreen and skin protection
Eyes	Corneal deposits 100% Optic neuritis <1%		Examination at baseline if there is an underlying abnormality, examinations thereafter as needed	Avoid or stop in presence of optic neuritis

Thyroid

Amiodarone may lead to both hypo- and hyperthyroidism. Patients who already have thyroid abnormalities, such as nodular goitre or Hashimoto's disease, are likely to have a higher risk of complications.

Amiodarone-induced hypothyroidism is more common in iodine-sufficient countries and typically occurs within the first two years of therapy. It is treated with thyroxine to normalise the concentrations of thyroid-stimulating hormone.

Amiodarone-induced thyrotoxicosis can occur suddenly and at any time during treatment. The management includes stopping amiodarone, and considering antithyroid therapy, prednisone or surgical thyroidectomy.[20,21]

Thyroid dysfunction may be asymptomatic, particularly in older patients,[22] and therefore the diagnosis should be based on biochemical tests. Clinical and laboratory assessments are needed at the start of treatment. Thyroid function should be monitored every six months. Clinical symptoms or changes in cardiac function should also prompt evaluation of thyroid function.

Skin

Photosensitivity is common following treatment with amiodarone. All patients should be cautioned to use sunscreen and cover exposed skin. Blue skin discolouration can occur, but typically resolves several months after stopping amiodarone.

Lungs

Pulmonary toxicity occurs in approximately 2–5% of patients taking amiodarone and is the adverse effect most associated with increased mortality.[23] The death rate ranges from 9% in patients who develop a chronic pneumonia to 50% in those with acute respiratory distress syndrome.[24]

Pulmonary toxicity is more common in older patients and in patients with underlying lung pathology.[1,19] It increases threefold for every 10 years of age in patients over 60 years old compared with those under 60 years.[24] Toxicity can occur at any time during the course of treatment. Those at the greatest risk are patients who have taken a daily dose of 400 mg or more for more than two months, or a lower dose, commonly 200 mg daily, for more than two years.[25]

Common presentations include acute or subacute cough and progressive dyspnoea.[20] Routine screening is of limited value as symptoms can develop rapidly. Patients who present with new respiratory symptoms should be promptly investigated.[26]

Pulmonary function tests typically show restriction as well as a decreased diffusing capacity of the lungs for carbon monoxide (DLCO). High resolution CT of the chest generally reveals diffuse ground glass and reticular abnormalities.

The treatment of pulmonary toxicity involves stopping amiodarone and often giving corticosteroids. Prolonged courses may be needed because of the long half-life of amiodarone.

Heart

Sinus node dysfunction and conduction disease are common in older patients so a careful assessment is needed before starting amiodarone.[27,28] Bradycardia and heart block occur in 1–3% of patients treated with amiodarone. Its use is therefore relatively contraindicated in patients with second- or third-degree heart block who do not have a pacemaker.

Gut

The gastrointestinal effects of amiodarone include nausea, anorexia and constipation. They can occur in up to 30% of patients and are more common in older people. The effects tend to improve with dose reduction.[3]

Liver

Hepatic toxicity occurs commonly in patients receiving long-term amiodarone. Liver enzymes should be checked every six months.[3] If concentrations reach three times the upper limit of normal, amiodarone should be discontinued, unless the patient has a life-threatening arrhythmia.

Other adverse effects

Neurological toxicity associated with amiodarone can include ataxia, paraesthesia and tremor. In a frail older patient these effects could increase the risk of falls. These neurological effects are often dose-related and improve when the dose is reduced.

Corneal microdeposits are visible on slit lamp examination in nearly all patients treated with amiodarone for three months. These deposits rarely affect vision or necessitate discontinuation of amiodarone.[21] Optic neuropathy and optic neuritis have been described in a small number of patients, however a causal relationship has not been well established.

Conclusion

In older adults, the use of toxic drugs for non-life-threatening indications should always be avoided. Amiodarone is a highly effective antiarrhythmic, however its unpredictable pharmacodynamics and broad adverse-effect profile make it a challenging drug to use safely in clinical practice. Its use should be reviewed in older patients with multiple comorbidities. Safer alternative drugs should be used preferentially in older patients with atrial fibrillation or minor ventricular arrhythmias, such as ventricular ectopy and non-sustained ventricular tachycardia.

When ongoing treatment with amiodarone is required for older patients, care should be taken to use the lowest effective dose. Patients often require dose reductions as they age, in consultation with the patient's cardiologist.

Regular monitoring of liver and thyroid function and pulmonary symptoms is required to identify complications at an early stage. Amiodarone toxicity often presents atypically and insidiously, particularly in older patients. New symptoms in a patient taking amiodarone should always be considered as potential adverse effects. ≺

Conflict of interest: none declared

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SELF-TEST QUESTIONS

True or false?

1. Amiodarone is the preferred drug for rate control in atrial fibrillation.
2. The development of corneal microdeposits is an indication to stop amiodarone.

Answers on page 175

REFERENCES

1. Vassallo P, Trohman RG. Prescribing amiodarone: an evidence-based review of clinical indications. JAMA 2007;298:1312-22. https://doi.org/10.1001/jama.298.11.1312
2. Kilborn MJ, Rathore SS, Gersh BJ, Oetgen WJ, Solomon AJ. Amiodarone and mortality among elderly patients with acute myocardial infarction with atrial fibrillation. Am Heart J 2002;144:1095-101. https://doi.org/10.1067/mhj.2002.125836
3. Vorperian VR, Havighurst TC, Miller S, January CT. Adverse effects of low dose amiodarone: a meta-analysis. J Am Coll Cardiol 1997;30:791-8. https://doi.org/10.1016/S0735-1097(97)00220-9
4. Campbell TJ. Amiodarone. Aust Prescr 2005;28:150-4. https://doi.org/10.18773/austprescr.2005.112
5. Al-Khatib SM, LaPointe NM, Curtis LH, Kramer JM, Swann J, Honig P, et al. Outpatient prescribing of antiarrhythmic drugs from 1995 to 2000. Am J Cardiol 2003;91:91-4. https://doi.org/10.1016/S0002-9149(02)03008-4
6. Steinberg BA, Hellkamp AS, Lokhnygina Y, Halperin JL, Breithardt G, Passman R, et al.; ROCKET AF Steering Committee and Investigators. Use and outcomes of antiarrhythmic therapy in patients with atrial fibrillation receiving oral anticoagulation: results from the ROCKET AF trial. Heart Rhythm 2014;11:925-32. https://doi.org/10.1016/j.hrthm.2014.03.006

7. Nantsupawat T, Nugent K, Phrommintikul A. Atrial fibrillation in the elderly. Drugs Aging 2013;30:593-601. https://doi.org/10.1007/s40266-013-0094-8
8. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al.; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002;347:1825-33. https://doi.org/10.1056/NEJMoa021328
9. Steinberg JS, Sadaniantz A, Kron J, Krahn A, Denny DM, Daubert J, et al. Analysis of cause-specific mortality in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) study. Circulation 2004;109:1973-80. https://doi.org/10.1161/01.CIR.0000118472.77237.FA
10. Qin D, Leef G, Alam MB, Rattan R, Munir MB, Patel D, et al. Mortality risk of long-term amiodarone therapy for atrial fibrillation patients without structural heart disease. Cardiol J 2015;22:622-9. https://doi.org/10.5603/CJ.a2015.0055
11. Brieger D, Amerena J, Attia J, Bajorek B, Chan KH, Connell C, et al.; NHFA CSANZ Atrial Fibrillation Guideline Working Group. National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand: Australian clinical guidelines for the diagnosis and management of atrial fibrillation 2018. Heart Lung Circ 2018;27:1209-66. https://doi.org/10.1016/j.hlc.2018.06.1043
12. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death. Circulation 2018;138:e272-391. https://doi.org/10.1161/CIR.0000000000000549
13. Stäubli M, Troendle A, Schmid B, Balmer P, Kohler B, Studer H, et al. Pharmacokinetics of amiodarone, desethylamiodarone and other iodine-containing amiodarone metabolites. Eur J Clin Pharmacol 1985;29:417-23. https://doi.org/10.1007/BF00613455
14. Price SD, Holman CD, Sanfilippo FM, Emery JD. Impact of specific Beers Criteria medications on associations between drug exposure and unplanned hospitalisation in elderly patients taking high-risk drugs: a case-time-control study in Western Australia. Drugs Aging 2014;31:311-25. https://doi.org/10.1007/s40266-014-0164-6
15. Neuffer EM, Tofade TS, Galpin LE. Significant bleeding in elderly patient with atrial fibrillation due to probable interaction between dabigatran and amiodarone. J Pharm Technol 2012;28:139-45. https://doi.org/10.1177/875512251202800402
16. Howell D, Hoch E, Shulman E, DiBiase L, Ferrick KJ, Fisher JD, et al. Interaction between amiodarone and rivaroxaban and the risk of major bleeding. Heart Rhythm 2016;13:S512. https://doi.org/10.1016/j.hrthm.2016.03.031
17. Flaker G, Lopes RD, Hylek E, Wojdyla DM, Thomas L, Al-Khatib SM, et al.; ARISTOTLE Committees and Investigators. Amiodarone, anticoagulation, and clinical events in patients with atrial fibrillation: insights from the ARISTOTLE trial. J Am Coll Cardiol 2014;64:1541-50. https://doi.org/10.1016/j.jacc.2014.07.967
18. Libersa CC, Brique SA, Motte KB, Caron JF, Guédon-Moreau LM, Humbert L, et al. Dramatic inhibition of amiodarone metabolism induced by grapefruit juice. Br J Clin Pharmacol 2000;49:373-8. https://doi.org/10.1046/j.1365-2125.2000.00163.x
19. Ernawati DK, Stafford L, Hughes JD. Amiodarone-induced pulmonary toxicity. Br J Clin Pharmacol 2008;66:82-7. https://doi.org/10.1111/j.1365-2125.2008.03177.x
20. Goldschlager N, Epstein AE, Naccarelli GV, Olshansky B, Singh B, Collard HR, et al.; Practice Guidelines Sub-committee, North American Society of Pacing and Electrophysiology (HRS). A practical guide for clinicians who treat patients with amiodarone: 2007. Heart Rhythm 2007;4:1250-9. https://doi.org/10.1016/j.hrthm.2007.07.020
21. Pollak PT. Clinical organ toxicity of antiarrhythmic compounds: ocular and pulmonary manifestations. Am J Cardiol 1999;84 Suppl 1:37-45. https://doi.org/10.1016/S0002-9149(99)00700-6
22. Gheri RG, Pucci P, Falsetti C, Luisi ML, Cerisano GP, Gheri CF, et al. Clinical, biochemical and therapeutical aspects of amiodarone-induced hypothyroidism (AIH) in geriatric patients with cardiac arrhythmias. Arch Gerontol Geriatr 2004;38:27-36. https://doi.org/10.1016/S0167-4943(03)00080-3
23. Olshansky B, Sami M, Rubin A, Kostis J, Shorofsky S, Slee A, et al.; NHLBI AFFIRM Investigators. Use of amiodarone for atrial fibrillation in patients with preexisting pulmonary disease in the AFFIRM study. Am J Cardiol 2005;95:404-5. https://doi.org/10.1016/j.amjcard.2004.09.044
24. Papiris SA, Triantafillidou C, Kolilekas L, Markoulaki D, Manali ED. Amiodarone: review of pulmonary effects and toxicity. Drug Saf 2010;33:539-58. https://doi.org/10.2165/11532320-000000000-00000
25. Wolkove N, Baltzan M. Amiodarone pulmonary toxicity. Can Respir J 2009;16:43-8. https://doi.org/10.1155/2009/282540
26. Siddoway LA. Amiodarone: guidelines for use and monitoring. Am Fam Physician 2003;68:2189-96.
27. Dekker LR. Treatment of atrial fibrillation in the elderly: time for a change? Neth Heart J 2011;19:403-4. https://doi.org/10.1007/s12471-011-0194-1
28. Essebag V, Hadjis T, Platt RW, Pilote L. Amiodarone and the risk of bradyarrhythmia requiring permanent pacemaker in elderly patients with atrial fibrillation and prior myocardial infarction. J Am Coll Cardiol 2003;41:249-54. https://doi.org/10.1016/S0735-1097(02)02709-2