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Management of Cardiac Rhythm Disturbances in the Ageing Heart

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ABSTRACT

The elderly experience a high proportion of chronic diseases, of which cardiac rhythm disturbances comprise a significant portion. Due to ageing-related metabolic and physiological changes, the management of cardiac rhythm disturbances will need to be modified and it is essential to be aware of the pharmacodynamics and pharmacokinetics of the drugs used. Non-drug treatment modalities, such as implantable cardioverter-defibrillators or radiofrequency ablation, which are increasingly available for use in the elderly, need to be considered periodically. The critical applications of drug and non-drug therapy of cardiac arrhythmias in the elderly are discussed in this article.

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INTRODUCTION

The multitude of changes in the body resulting from the ageing process can significantly impact on the management of cardiac arrhythmias that manifest throughout life, but are most prominent in those aged 75 years and above.¹

METABOLIC AND PHYSIOLOGICAL CHANGES

Ageing-related metabolic and physiological changes affect total body water, intravascular volume, fat to muscle ratio and body composition, all of which influence the volume of distribution for drugs.² The proportion of body fat increases with ageing and causes an increase in the volume of distribution, leading to delayed steady state and the onset of peak effect or toxicity of lipophilic drugs, such as some beta-blockers, resulting in the drug's prolonged half-life and duration of action. The standard adult loading doses of hydrophilic drugs, such as digoxin, display an enhanced effect or toxicity due to the reduction in lean body mass and total body water. Once steady state is achieved with chronic dosing of hydrophilic drugs, the drug elimination rate determines the plasma level and the drug response.

Although the decline in glomerular filtration rate generally begins around the age of 30 years, significant changes in serum creatinine occur later in life. In the elderly, normal serum creatinine level does not imply a normal glomerular filtration rate and renally eliminated drugs can potentially cause toxicity due to accumulation of the drugs or their metabolites. The glomerular filtration

rate can further vary by as much as 20% in chronically ill and debilitated patients and the renal elimination of drugs such as sotalol, flecainide and atenolol, becomes unpredictable, more so during an intercurrent illness.

Due to ageing, the liver mass, hepatic blood flow and metabolic capacity may also decrease and result in higher serum concentrations at similar doses of drugs, such as verapamil, lignocaine and diltiazem, when compared with a younger adult. The rate of hepatic oxidative drug metabolism can be altered (induced or inhibited) by alcohol or other concomitant medications which affects prediction of drug effect or toxicity and is further compounded by age-independent genetic variability of metabolism.

Decreased serum albumin, due to illness or decreased protein synthesis (due to ageing), potentiates the response to drugs that bind to albumin by increasing the free-drug fraction in the acute condition. Therefore, drug levels or response correlation could be altered and this needs to be considered when interpreting drug levels especially during long-term usage. An elevated level of the acute phase reactant α_1 -acid glycoprotein, due to ageing or disease, increases the binding of basic drugs, such as lignocaine, which in turn decreases the drug response.

Age-related changes in the various organ systems could also be attributed to the 'wear and tear' (cumulative oxidative damage and inflammatory response), hormonal perturbations and programmed cell death or apoptosis.

CARDIAC CHANGES

Increased left atrial size and premature atrial beats are commonly seen with ageing, as well as decreased maximal heart rate or beat-to-beat heart rate variability, increased atrioventricular node conduction time or decreased baroreflex function along with increased sensitivity to parasympathetic stimulation. In addition, the senescent myocardium is susceptible to arrhythmias due to calcium overload caused by abnormalities of calcium handling, which could be compounded by ischaemia or drugs. Decreased beta-adrenoceptor density related to altered G-protein coupling or signal transduction of ageing could occur causing abnormal homeostatic responses to posture and/or drugs.

Coexisting disease and multi-organ dysfunction of ageing should be taken into consideration as polypharmacy becomes necessary and disease-drug or drug-drug interactions increase morbidity and mortality. Polypharmacy is a well known risk factor for adverse drug reactions.³ Long-term administration of multiple drugs increases the risk of adverse effects.⁴ Moreover, although the elderly belong to an age group at the highest

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risk of adverse drug reactions they are under-represented in drug trials.^{5,6} In addition, neurological, visual and auditory disabilities of ageing affect compliance. The risk-benefit ratio of therapeutic interventions can be less favourable in the elderly and discretion is warranted.

ANTIARRHYTHMIC DRUGS

Antiarrhythmic drugs carry a significant risk of proarrhythmia along with other cardiovascular and non-cardiovascular adverse effects (Table 1). Drugs with a low therapeutic index, such as digoxin, or drugs predominantly renally cleared, such as sotalol, should be started at low doses. Although most cardiac drugs can be used in the elderly, amiodarone and digoxin must be used with caution and at low doses, and the planned duration of therapy reassessed periodically.⁷ Dosages of antiarrhythmic drugs are monitored predominantly on clinical grounds, but from time to time drug levels are required for optimising care and avoiding toxicity, e.g. serum digoxin levels are useful in determining toxicity. Antiarrhythmic drugs have been traditionally classified as possessing one or more of the four classes of antiarrhythmic action described by Vaughan Williams.

Class I Antiarrhythmic Drugs

Class I antiarrhythmic drugs predominantly block fast sodium channels and decrease the excitability of cardiac myocytes. Class I drugs are further subclassified into IA, IB and IC according to effects on the cardiac action potential upstroke, action potential duration and refractory period.

Class IA Antiarrhythmic Drugs

Class IA drugs are no longer in common use in Australia. Class IA drugs, such as disopyramide, have anticholinergic and negative inotropic properties and should be used with caution in the elderly.

Class IB Antiarrhythmic Drugs

Lignocaine may be administered intravenously for managing recurrent malignant ventricular arrhythmias in acute myocardial infarction. Decreased hepatic blood flow of ageing dictates use of lower infusion rates for lignocaine, especially in the presence of heart failure.

Mexiletine is similar to lignocaine in most of its effects, is administered orally and can be used in the treatment of ventricular arrhythmias, usually combined with amiodarone or sotalol when monotherapy is inadequate. A significant number of patients on mexiletine develop neurological adverse effects such as tinnitus, diplopia and dysarthria. Mexiletine has a low therapeutic index and should be used with caution.

Class IC Antiarrhythmic Drugs

Flecainide is useful for ventricular and supraventricular arrhythmias but is contraindicated in the presence of structural heart disease including coronary heart disease.⁸ To prevent increased ventricular rates in atrial flutter or atrial fibrillation, flecainide should always be combined with a heart rate slowing drug, such as a beta-blocker, diltiazem or verapamil. The pro-arrhythmic effects of flecainide are well known.^{9,10} Flecainide is more effective than some of the other class I drugs in preventing recurrence of atrial fibrillation but may cause prolongation of the QRS duration especially at high rates and on exercise testing, the finding of a QRS duration above 0.2 seconds suggests flecainide toxicity.

Class II Antiarrhythmic Drugs

Class II antiarrhythmic drugs inhibit the effect of adrenergic stimulation by blocking beta-adrenoceptors and decreasing heart rate and intracellular calcium overload. Class II drugs are used for supraventricular and ventricular arrhythmias as well as for the control of ventricular rate in atrial fibrillation.

Beta-Blockers

Beta-blockers mitigate the impact of catecholamine excess and sympathetic nervous system stimulation, which is important in the genesis of many arrhythmias. Beta-blockers have been shown to lower mortality after myocardial infarction and are useful in conditions with prolonged QT interval.^{11,12} In addition, beta-blockers, such as carvedilol, bisoprolol and slow-release metoprolol, are of prognostic benefit in patients with systolic heart failure and decrease the incidence of ventricular arrhythmias. Although propranolol, a non-selective beta-blocker, is now less commonly used, it

Table 1. Commonly used antiarrhythmic drugs

Drug	Elimination route	IV loading dose	IV maintenance dose	Oral maintenance dose	Therapeutic blood level*	Half-life*
Lignocaine	Liver	0.5-2 mg/kg at 20-50 mg/min	10-50 microg/kg/min	-	1-5 microg/mL	1-2 h
Amiodarone	Liver	150 mg over 10 min, 1 mg/min for 3 h, then 0.5 mg/min; (oral 200-400 mg thrice daily for 1 week, twice daily for 1 week, then maintenance dose)	15-20 mg/kg over 24 h	100-400 mg daily (usual 200 mg daily); AF 100 mg daily if > 3 months use	0.5-1.5 microg/mL	56 days
Verapamil	Liver	5-10 mg over 1-2 min	-	160-240 mg daily	0.1-0.15 microg/mL	3-8 h
Adenosine	-	6-18 mg rapidly for acute termination of SVT	-	-	-	-
Digoxin†	Kidney	0.25 mg (if needed repeat after 6 h)	-	0.625-0.25 mg daily (consider alternative in renal impairment)	0.6-1.0 nmol/L	36-48 h
Sotalol	Kidney	-	-	80-160 mg 12-hourly	-	12 h

*Normal adults; †Rathore SS, Curtis JP, Wang Y, Bristow MR, Krumholz HM. Association of serum digoxin concentration and outcomes in patients with heart failure. JAMA 2003; 289: 871-8.

AF = atrial fibrillation; IV = intravenous; SVT = supraventricular tachyarrhythmia

still has a place for arrhythmias resulting from digoxin toxicity, phaeochromocytoma and thyrotoxicosis. Beta-blockers can cause significant bradycardia, precipitate heart failure or cause bronchospasm in susceptible patients. Beta-blockers should be started at low doses, followed by cautious upward titration to maximally useful doses.

Class III Antiarrhythmic Drugs

Class III antiarrhythmic drugs block potassium channels and prolong repolarisation. Class III drugs, such as ibutilide and dofetilide, are not available in Australia.

Amiodarone

Amiodarone has complex electrophysiological effects, a long half-life and antiarrhythmic as well as pro-arrhythmic effects. In addition to its effect on potassium channels, amiodarone also blocks sodium channels, calcium channels and beta-adrenoceptors. Amiodarone is used for a wide range of arrhythmias including atrial fibrillation, atrial flutter and life-threatening ventricular arrhythmias, especially when other drugs have failed or in selected patients after the implantation of implantable cardioverter-defibrillators.¹³ Amiodarone toxicity involves various organ systems, such as skin (photosensitivity), thyroid gland (hypothyroidism, hyperthyroidism), liver and rarely the lungs. QT interval prolongation and torsades de pointes have been reported rarely (incidence < 1%) with amiodarone use. A chest radiograph, pulmonary function and lung carbon monoxide diffusion capacity tests are recommended at baseline and annually thereafter to screen for toxicity in patients on long-term amiodarone. Thyroid function should be tested every six months.

Sotalol

Sotalol, a non-selective beta-blocker with repolarisation prolonging effects, is useful in life-threatening ventricular tachyarrhythmias, atrial fibrillation and other supraventricular tachyarrhythmias. Sotalol prolongs atrial and ventricular refractory periods, the QT interval as well as sinus cycle length. Sotalol is well tolerated but can cause torsades de pointes (5% incidence when used for ventricular arrhythmias). Sotalol should be used cautiously in the presence of left ventricular systolic dysfunction because of its beta-adrenoceptor blocking effect and the risk of precipitating heart failure.

Class IV Antiarrhythmic Drugs

Class IV antiarrhythmic drugs, such as verapamil and diltiazem, block slow calcium channels and are useful for supraventricular tachycardia and in slowing the ventricular rate of atrial fibrillation or atrial flutter. Hypotension and significant bradyarrhythmias may occur in patients on concomitant beta-blockers or with pre-existing sinus node or atrioventricular node dysfunction. The class IV drugs are contraindicated in the presence of pre-existing heart failure or atrioventricular block.

Other Antiarrhythmic Drugs

Adenosine

Adenosine, an endogenous nucleoside is used in the acute management of supraventricular tachycardia. To be effective, adenosine should be administered by rapid intravenous injection followed by a rapid saline flush, especially when using peripheral venous access.

Adenosine shortens the atrial action potential duration and hyperpolarises the atrial membrane potential. Similar changes are also produced in both the sinus and atrioventricular nodes. The resultant transient atrioventricular node block terminates atrioventricular node dependent supraventricular tachyarrhythmias. Other supraventricular tachyarrhythmias and some ventricular tachycardias may occasionally be terminated by adenosine.

Digoxin

Digoxin acts primarily by enhancing the central and peripheral vagal tone. Digoxin can be used for ventricular rate control in chronic atrial fibrillation, although it is of limited benefit in controlling the increase in heart rate seen with physical exertion. Digoxin toxicity can result in arrhythmias due to a markedly enhanced parasympathetic tone and delayed after depolarisations. Advanced age, hypokalaemia, chronic lung disease, hypothyroidism and amyloidosis increases sensitivity to digoxin. Digoxin use requires a thorough knowledge of interactions with other antiarrhythmic drugs. Patients' digoxin levels need to be monitored regularly to avoid toxicity especially when the glomerular filtration rate is decreased or when digoxin is used in conjunction with other antiarrhythmic drugs, such as verapamil, diltiazem and amiodarone.

CARDIAC RHYTHM DISTURBANCES

Management of the elderly with cardiac rhythm abnormalities is largely similar to younger adults.

Bradyarrhythmias

In the elderly, sinus bradycardia is often asymptomatic and usually does not need treatment. Sinus bradycardia may be induced by drugs, such as beta-blockers, or the negatively chronotropic calcium channel blockers. Light-headedness and syncope can also occur, especially when parasympathetic overactivity of ageing coexists, necessitating withdrawal of the offending drugs.

Sinus node dysfunction, carotid hypersensitivity, sinoatrial exit block, atrioventricular block, hypokalaemia, hypothyroidism and drug toxicity can cause bradycardia and may be reversible with treatment. Bolus intravenous atropine followed by isoprenaline infusion or transvenous temporary pacing may be needed in an emergency situation for acutely symptomatic or haemodynamically unstable patients. The indications to implant a permanent pacemaker are outlined in the recent American College of Cardiology, American Heart Association and Heart Rhythm Society guidelines for pacing.¹⁴

Tachyarrhythmias

The management of tachyarrhythmias is guided by their electrophysiological basis.^{15,16} Increased automaticity, re-entry or triggered activity (early or delayed after depolarisation) form the electrophysiological basis of tachyarrhythmias.

Sinus Tachycardia

Sinus tachycardia can be caused by sepsis, blood loss, enhanced sympathetic activity and thyrotoxicosis, and will respond to the treatment of the primary condition. Beta-blockers, diltiazem or verapamil may be used in certain circumstances for slowing the sinus rate in patients with inappropriate sinus tachycardia. In patients with refractory sinus tachycardia, ivabradine (blocks the

pacemaker I_f current responsible for the spontaneous diastolic depolarisation in the sinoatrial node), sinus node modification or radiofrequency ablation have been tried with some success.^{17,18}

Atrial Ectopy

Frequent premature atrial complexes do not usually need treatment except in very symptomatic patients. In these circumstances, beta-blockers, diltiazem or verapamil can be used.

Atrial Fibrillation

Atrial fibrillation is the most common rhythm disturbance seen in the elderly with a prevalence of 8% in those above 80 years of age.¹⁹ Symptoms of atrial fibrillation may include palpitations, dyspnoea, fatigue or exercise intolerance. Tachycardia-induced left ventricular dysfunction can result if rapid ventricular rates persist for a prolonged period. The two broad strategies used in managing atrial fibrillation are rhythm control (restore and/or maintain sinus rhythm) or rate control (limit symptoms by controlling the ventricular rate). There is no survival advantage with either strategy, although a rate control strategy resulted in fewer hospitalisations and adverse drug effects in the Atrial Fibrillation Follow-Up Investigation of Rhythm Management study.²⁰ The choice of strategy will depend on factors such as the presence and severity of symptoms, associated comorbidities, haemodynamic consequences of atrial fibrillation and risk of adverse drug effects.²¹⁻²⁵

Ventricular rate control rather than rhythm control is often appropriate for the older asymptomatic or minimally symptomatic patient with persistent atrial fibrillation. Class II or IV drugs, such as beta-blockers, are useful unless they are contraindicated because of either left ventricular systolic dysfunction or the presence of asthma. Digoxin does not effectively control ventricular rate in the presence of sympathetic stimulation as occurs during exercise but can be useful in the presence of heart failure and if required in combination with amiodarone to optimise rate control without compromising left ventricular systolic function.

Rhythm control may be preferred in selected symptomatic patients using electrical cardioversion, antiarrhythmic drugs or radiofrequency ablation for failed antiarrhythmic drug therapy.²⁶ In symptomatic atrial fibrillation, elective electrical cardioversion with or without additional antiarrhythmic drugs (to enhance success) combined with adequate anticoagulation, if not contraindicated (international normalised ratio of 2 to 3 for at least 4 weeks prior and 4 weeks after cardioversion) could be considered, but maintenance of sinus rhythm is unpredictable.²⁷ Transoesophageal echocardiography to rule out left atrial thrombus has been used to avoid the pre-cardioversion anticoagulation waiting period, but it may not altogether eliminate the risk of thromboembolism. Permanent pacemaker implantation followed by atrioventricular node radiofrequency ablation with lifelong anticoagulation is indicated when other drug measures fail or are deemed unsuitable, especially when tachycardia-induced cardiomyopathy is suspected. The presence of atrial fibrillation carries a thromboembolic risk and the CHADS₂ (clinical prediction rule for estimating the risk of stroke in non-rheumatic or non-valvular atrial fibrillation) scoring system can assist in determining the degree of risk as well as guide in the decision regarding the use of warfarin.²⁸

Atrial Flutter

Rate control of atrial flutter is more difficult than in atrial fibrillation. Overdrive pacing, when available, is a good option for terminating atrial flutter.¹⁵ Anticoagulation for atrial flutter is indicated and class IA or IC drugs (in combination with atrioventricular node slowing drugs) or class III drugs can be used.²⁹⁻³¹ Radiofrequency ablation is an excellent therapeutic option for macro re-entrant atrial flutter in suitable patients.

Multi-Focal Atrial Tachycardia

Multi-focal atrial tachycardia is typified by atrial rates of 100 to 130 beats/minute and variation in the P wave morphology on the electrocardiogram. Multi-focal atrial tachycardia is more commonly seen in the elderly due to digoxin toxicity or chronic pulmonary disease.^{32,33} Treatment of the underlying cause with the addition of either a beta-blocker in the absence of airways disease, verapamil or amiodarone is appropriate.

Atrioventricular Nodal Re-Entrant Tachycardia

Atrioventricular nodal re-entrant tachycardia is the commonest cause of a regular supraventricular tachycardia and can usually be terminated with vagal manoeuvres or intravenous adenosine in the acute setting. Calcium channel blockers, beta-blockers, flecainide, sotalol or amiodarone can be used to prevent recurrent episodes with the less toxic drugs used as first-line in uncomplicated cases. Radiofrequency ablation can be curative with low risk of complications.

Ventricular Ectopy

Ventricular premature beats generally need no treatment. Class I or III drugs carry the risk of pro-arrhythmia and should be avoided. The Cardiac Arrhythmia Suppression Trial involved patients with a prior myocardial infarction and had to be prematurely discontinued after recruiting 2309 patients as treatment with the class IC drugs resulted in a high mortality.⁸ Approximately 35% of these patients were older than 66 years of age.

Ventricular Tachycardia

Haemodynamically tolerated ventricular tachycardia or polymorphic ventricular tachycardia without evidence of a prolonged QT interval can be treated with bolus intravenous amiodarone (preferably lignocaine in the presence of myocardial ischaemia) followed by an intravenous amiodarone infusion.³⁴ Magnesium sulfate is useful in patients with long QT intervals and episodes of torsades de pointes.³⁵ Metabolic abnormalities should be corrected, especially hypomagnesaemia or hypokalaemia. As is the case with other sustained arrhythmias, immediate direct current cardioversion is indicated in the presence of haemodynamic compromise.

Multiple trials have demonstrated the superiority of implantable cardioverter-defibrillators over drugs in the prevention of sudden cardiac death in patients at risk of life-threatening ventricular arrhythmias.³⁶⁻³⁹ In the Sudden Cardiac Death in Heart Failure Trial, 2521 patients (median age 60 years) with New York Heart Association class II to III congestive heart failure on conventional therapy and a left ventricular ejection fraction below 35% were randomly assigned placebo, amiodarone or an implantable cardioverter-defibrillator.³⁸ This study demonstrated that implantable cardioverter-defibrillators (primary prevention trial) reduced overall mortality by 33%, while amiodarone had no favourable effect on survival.

Numerous studies have shown the usefulness of beta-blockers in patients with decreased left ventricular systolic function.¹¹ The retrospective analysis of the patients from the Cardiac Arrhythmia Suppression Trial for effect of beta-blocker therapy showed a significantly enhanced survival at 30 days, and at one to two years of follow-up against all-cause and arrhythmic death or non-fatal cardiac arrest in patients of whom 35% were in the over 65 years age group.¹²

For patients who have survived cardiac arrest or patients with prior sustained ventricular tachycardia and poor left ventricular function, an implantable cardioverter-defibrillator is the treatment of choice and long-term empirical amiodarone is a good option when an implantable cardioverter-defibrillator is not feasible.^{13,40} Median survival in octogenarian recipients of implantable cardioverter-defibrillators was greater than four years in one study.^{41,42} However, in an elderly patient, the decision to use an implantable cardioverter-defibrillator needs to be carefully considered as such therapy is expensive and has its own risks. Implantable cardioverter-defibrillators are contraindicated in patients with a life expectancy of less than one year. Radiofrequency ablation is available for some forms of ventricular tachycardia, in the appropriate clinical situation. Incessant or repetitive ventricular tachyarrhythmias requiring defibrillation need to be treated with antiarrhythmic drugs and occasionally radiofrequency ablation is beneficial.

Ventricular Flutter or Ventricular Fibrillation

Immediate non-synchronised direct current biphasic shock is mandatory therapy for ventricular flutter or ventricular fibrillation. Implantable cardioverter-defibrillators may be useful for secondary prevention of sudden death.

CONCLUSION

The management of arrhythmias in the elderly warrants a clear understanding of their age-related differences, comorbidities, drug–drug and drug–disease interactions as well as treatment tolerability. Many new drugs are undergoing evaluation but further research focusing on the older cohort is needed.

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The material in this article has been accredited by SHPA as suitable for inclusion in an individual pharmacist's CPD plan as outlined in the **shpacpd** program <www.shpa.org.au/docs/cpd.html>. A series of questions that can assist you with evaluating your learning outcomes can also be found on the SHPA web site. Answers to these questions can be lodged until December 2009 at <www.shpa.org.au/docs/cpd.html> .

In **shpacpd** this is considered an Activity Group 2 activity: Improving Knowledge and Skills with assessment. The number of hours will be dependent on the time you have taken to read the article, complete the multiple choice questions and submit the answers.
