<R/Heads>PHARMACOLOGY

Drugs acting on the heart: anti-arrhythmics

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Learning Objectives

After reading this article, you should be able to:

- draw the cardiac myocyte and pacemaker action potential, and link these to anti-arrhythmic sites of action
- identify at least five common causes of arrhythmias
- give named examples of the major classes of anti-arrhythmic drugs, along with their site and mechanism of action
- describe the evidence in relation to the treatment of common arrhythmias

Abstract

Arrhythmias can occur in medical or surgical practice and are common in the perioperative period and in intensive care. Their occurrence may reflect a pre-existing condition or predisposition, or arise *de novo*. Arrhythmias must be identified promptly and managed appropriately as they may become unstable, compromise cardiac output and risk cardiac arrest. In many cases, this involves prevention or correction of precipitating factors and sometimes non-pharmacological treatments (cardioversion or surgical ablation). However, anti-arrhythmic drugs are often required. A sound understanding of drug mechanisms, guidelines and evidence will aid choice of therapy. This article describes the mechanisms of action of the common anti-arrhythmic agents, their use in clinical practice and a review of recent guidelines for the management of common arrhythmias.

Keywords amiodarone; anti-arrhythmia agents; arrhythmias, cardiac; digoxin; lidocaine; magnesium

Introduction

The normal contraction of the myocardium requires organised initiation and conduction of electrical activity (Figure 1). The depolarisation of the myocardium is initiated via the sino-atrial node (SAN). This pacemaker generates a depolarising impulse which passes to the atrio-ventricular node (AVN), the His-Purkinje system and finally to the ventricles. Abnormal cardiac rhythms are caused by abnormalities of impulse generation, impulse conduction or both. They may originate from any part of this system, and may be congenital or acquired in nature.

Symptoms may range from none (asymptomatic) to acute cardiovascular collapse. To understand arrhythmias and their treatment, it is helpful to review the normal electrophysiology of the cardiac myocyte and conducting system (Figure 1).

Classification

Anti-arrhythmic drugs have been traditionally classified by the Vaughan-Williams system according to drug class and mode of action. However, this classification has limitations: it does not include all drugs with anti-arrhythmic properties, some drugs have more than one action, nor does it consider more recent, novel drugs.

Table 2 gives a functional classification of anti-arrhythmic agents, showing site and mode of action as well as the arrhythmias for which the drugs are indicated. The Vaughan-Williams classification is also given. In clinical practice, the treatment of arrhythmias depends on the extent to which the patient is compromised, the site of the arrhythmia (ventricular or supraventricular) and the potential for progression to an unstable tachyarrhythmia with Resuscitation Council (UK) Advanced Life Support guidelines providing the basis for stepwise assessment and therapy (1).

ALS guidelines recommend electrical synchronised DC cardioversion as first line treatment for all tachyarrhythmias, where features of instability (shock, syncope, myocardial ischaemia or heart failure) are present (1). Where the arrhythmia is stable, non-pharmacological methods (carotid sinus massage or Valsalva manoeuvre) are recommended, followed by drug therapy. Underlying causes (Table 1) should always be corrected if possible.

For persistent arrhythmias, where an electrophysiological or structural cause has been identified, surgical techniques (catheter ablation, implantable pacemakers/defibrillators) are preferred. These techniques are outside the scope of this article (see further reading: Liew 2013).

Mechanisms of drug action – cardiac electrophysiology

Figure 1 below show the cardiac action potential for the SAN and myocyte.

In general, sodium (Na^+) or calcium (Ca^{2+}) influx into myocytes and pacemaker cells causes the membrane potential to become less negative, and depolarisation promotes electrical activity, whereas potassium (K^+) efflux promotes hyperpolarisation and reduces electrical activity. Therefore, anti-arrhythmic agents promote membrane stabilisation by reducing these ionic movements within cells; blocking Na^+ or Ca^{2+} channels, ATPase pumps, or opening K^+ channels.

Figure 1 – link between myocardial contraction, electrical activity and contraction

The overall membrane potential is determined by the balance of intracellular and extracellular ion concentrations. Na^+ and Ca^{2+} influx contribute to depolarisation, whereas K^+ efflux contributes to hyperpolarisation and reduced excitability. Ca^{2+} and K^+ channels are influenced by autonomic nervous activity as well as hypoxia, temperature and drugs.

(ARP = Absolute refractory period, RRP = relative refractory period, TP = Threshold potential)

Which drug to use?

The first step is to diagnose the arrhythmia accurately and treat any underlying or precipitating factors (Table 1). Once the rhythm has been identified, the first question is whether or not the patient is stable. Arrhythmias may be acute, chronic, or represent progression of a previously stable chronic rhythm (for example AF with a fast ventricular rate in a patient with previously rate controlled AF). The first line treatment for a patient with an unstable tachyarrhythmia is urgent synchronised DC cardioversion. For emergency treatment of acute arrhythmias within the hospital setting, current Resuscitation Council (UK) algorithms are available from www.resus.org.uk (1).

For stable patients, a decision is made between nonpharmacological, pharmacological and electrical treatments; either to control the rate of the rhythm, or revert to sinus rhythm. Patients in AF for longer than 48 hrs require thromboprophylaxis to reduce their risk of stroke.

Most of the arrhythmias requiring urgent treatment are tachycardias, which is the focus of this article. The simplest way to classify tachycardias is by QRS duration as supraventricular or ventricular tachycardias.

Drugs to treat supraventricular tachycardias

Supraventricular arrhythmias arise in the atria, SAN or AVN. Management is directed at reducing the transmission frequency or electrical excitability in these pathways, by either antagonism at Na^+ or Ca^{2+} channels (opposes Phase 0), facilitation of K^+ channels (enhances Phase 3), or inhibiting repolarisation (Phase 4) (Figure 1).

Adenosine: a naturally occurring purine nucleoside that acts at specific A_1 and A_2 receptors. The effect in electrically active tissue is to induce hyperpolarisation by opening K^+ channels, which are coupled to the A_1 receptor via G_i . The effect in vascular smooth muscle, elicited by A_2 , is to increase cAMP through G_s . Hyperpolarisation of the SAN, AVN and conduction pathways induces a transient AV block, which may either cause cardioversion, or slow the heart rate to enable interpretation of the underlying rhythm. Enhancing K^+ efflux reduces the electrical excitability in pacemaker cells and myocytes (Figure 1), thereby stabilising cardiac rhythm. Adenosine has a half life of 10 seconds, and is given as a rapid intravenous bolus in escalating doses of 6mg followed by 12mg and a final dose of 12mg. Hyperpolarising normal electrically active tissue may enhance conduction along accessory pathways, and therefore it is contraindicated in Wolff-Parkinson White syndrome. Relative and absolute contraindications include asthma, sick sinus syndrome, decompensated heart failure, heart blocks and long Q-T syndrome. Due to the risks of profound bradycardia or potentiating arrhythmias, adenosine must be given with continuous cardiac monitoring.

Esmolol: a fast-onset (6 minutes), fast-offset (20 minutes), relatively selective β_1 -adrenoreceptor blocker. This causes a reduction in the rate of depolarisation of the SAN through blocking the G_s coupled β_1 -adrenoreceptor. This slows tachyarrhythmias in order to unmask the underlying rhythm or to cardiovert to sinus rhythm. It is given as an intravenous infusion (50–150 $\mu\text{g}/\text{kg}/\text{min}$), titrated to response. Esmolol is metabolised primarily by red cell esterases to methanol and an acid metabolite. Adverse effects include hypotension, bradycardia, bronchospasm and central nervous system disturbances.

Ibutilide: a pure class 3 drug acting on slow inward Na^+ channels, reducing the slope of Phase 0, thereby prolonging the action potential and refractory period. Ibutilide is commonly used for recent-onset AF (2). It is administered as an intravenous infusion over 10 minutes and repeated if necessary; the dose is dependent on weight (0.01 mg/kg as a slow IV bolus over 10 minutes,

repeatable for one further dose). It is metabolised by hepatic cytochrome P450 enzymes; adverse effects include chest pain and breathing difficulties.

Verapamil: causes a block of the AVN and slowing of cardiac rate by competitive blockade of the slow (T-type) Ca^{2+} channel, affecting Phase 0 of the pacemaker potential. This decreased Ca^{2+} influx decreases automaticity and increases the refractory period. It is used to treat paroxysmal SVTs, AF and atrial flutter. Verapamil can be given orally (240–480 mg/day in three divided doses) or intravenously (5–10 mg over 30 seconds). It is metabolised in the liver. Adverse effects include first- or second-degree heart block and VT/VF in patients with Wolff–Parkinson–White syndrome.

Digoxin: a glycoside that has direct and indirect effects. The direct effect is through inhibition of the Na^+/K^+ -ATPase prolongation of the refractory period via antagonism, thereby increasing $[\text{Na}^+]_i$ and decreasing $[\text{K}^+]_i$ and so prolongation of the refractory period. The increased intracellular $[\text{Na}^+]_i$ alters the equilibrium of the $\text{Na}^+/\text{Ca}^{2+}$ exchanger; thus causing a decrease in Ca^{2+} efflux and an increase in Ca^{2+} influx, leading to an increased $[\text{Ca}^{2+}]_i$. Decreased $[\text{K}^+]_i$ causes a slowing of atrioventricular conduction. Digoxin also enhances vagal activity causing indirect negative chronotropic effects. The vagal effects and reduced $[\text{K}^+]_i$ slow conduction through the AV node. An additional effect is to increase $[\text{Ca}^{2+}]_i$, increasing inotropy. This combination of effects is commonly used to treat atrial fibrillation and flutter.

The narrow therapeutic range of digoxin requires a loading regimen, dose monitoring and caution in renal failure. Therapeutic plasma concentrations must be monitored as digoxin toxicity causes several adverse effects, including junctional bradycardias, ventricular bigeminy, second- and third-degree heart block and visual disturbances. The dose is reduced in patients with renal failure, and toxicity is increased in the presence of hypokalaemia, hypomagnesaemia, hypernatraemia or hypercalcaemia. The loading dose of digoxin is 10–20 $\mu\text{g}/\text{kg}$ (orally or parenterally) in three divided doses at 6-hour intervals until the desired effect has been established, followed by maintenance doses of 10–20 $\mu\text{g}/\text{kg}/\text{day}$.

Amiodarone: has mechanisms of action common to class I, II and IV drugs affecting Na^+ and K^+ channels as well as β -adrenoceptors. Na^+ channel blockade causes hyperpolarisation at the SAN and AVN, prolonging the refractory period and action potential. K^+ channel blockade also prolongs the refractory period in pacemaker and myocyte cells (Figure 1). β -adrenoceptor blockade has a negative chronotropic effect at the SAN. This multimodal effect is suited to both supraventricular and ventricular arrhythmias. It is given as an intravenous bolus of 300 mg over 30 minutes, followed by 900 mg over 23 hours or orally by means of 100 or 200 mg tablets. It is metabolised by the liver to an active metabolite. It has many adverse effects during chronic administration, most notably pulmonary fibrosis, corneal micro deposits, thyroid disorders, cirrhosis and peripheral neuropathy. During acute administration, it can precipitate cardiovascular collapse and AV block. Dronedronone is a new analogue of amiodarone used in the management of cardiac arrhythmias and possesses fewer side effects.

Drugs to treat ventricular tachycardias

Ventricular arrhythmias represent abnormal foci of electrical activity in the ventricles. Treatment requires membrane stabilisation by reducing depolarisation, or increasing hyperpolarisation in these tissues; i.e. enhancing K^+ efflux, or reducing Na^+ or Ca^{2+} influx. These arrhythmias may be monomorphic (ventricular tachycardia) or polymorphic (torsades de pointes) depending on their origin. In a stable, conscious patient, anti-arrhythmic treatment depends on reducing excessive electrical activity.

Lidocaine: an amide local anaesthetic that causes blockade of Na^+ channels to reduce the excitability of electrically active tissues. Lidocaine is used in the treatment of ventricular tachycardias as an intravenous bolus of 1 mg/kg over 2 minutes, followed by an infusion of 4 mg/min for 1 hour, 2 mg/min for 1 hour and finally 1 mg/min for 1 hour. It is metabolised in the liver. Allergic reactions are rare; adverse effects that may indicate toxicity are perioral tingling, ectopic beats, respiratory depression and coma all of which are dose-dependent. Doses must not exceed 3 mg/kg intravenously.

Magnesium (Mg^{2+}): a cofactor in many enzyme systems including the Na^+/K^+ -ATPase. It antagonises atrial Ca^{2+} channels and inhibits K^+ channels, causing an increase in the refractory period. It is used to treat torsades de pointes and ventricular arrhythmias. Various dosing regimens exist (e.g. 16 mmol over 20 minutes intravenously), however the dose should be titrated to pre-existing Mg^{2+} levels and serum Mg^{2+} concentrations should be monitored closely. Fifty percent is excreted unchanged in the urine. Adverse effects include AV and intraventricular conduction disorders as well as muscular and respiratory weakness. Toxic effects of hypermagnesaemia can be overcome by administration of calcium.

Amiodarone: can be used to treat a variety of ventricular arrhythmias; its pharmacology is described above.

Novel drugs

Whilst the multi-modal effects of amiodarone are effective, its long term use can be limited by the range of adverse effects. Novel drugs targeted at multiple ionic currents but without the significant adverse effects may represent the future of antiarrhythmics. Drugs currently in testing and development include Vaughan-Williams class III drugs azimilide and vernakalant, and a novel agent ivabradine.

Azimilide and *vernakalant* are multi-channel blockers, inhibiting multiple ionic currents and stabilising electrically active tissues. Vernakalant has been approved for clinical practice and is reported to have a high success rate for cardioversion (3) by inhibiting atrial selective K^+ and Na^+ channels. It has been approved for use in non-surgical patients with AF of duration of seven days or fewer and in post-cardiac surgery patients with AF of duration of three days or fewer. Azimilide has been previously used for ventricular arrhythmias (4).

Ivabradine is a novel drug which acts on i_f (see Figure 1). This reduces the rate of pacemaker depolarisation and therefore this drug may be used for the control of supraventricular tachyarrhythmias. This drug is licensed for treatment of angina to reduce heart rate and therefore oxygen consumption. It also has a role in cardiac failure. However, the beneficial effect of reducing heart rate may also mean that this drug has applications as an anti-arrhythmic; this has been described (5) although further work is needed.

Table 1

Causes of arrhythmias in patients in intensive care or those undergoing anaesthesia

Anatomical	Physiological	Biochemical	Disease
Congenital	Cardiac ischaemia	Hypo/hyperkalaemia	Sepsis
Cardiac abnormality	Hypotension	Hypocalcaemia	Pneumonia
Mechanical (e.g. CVC/Hickman/PA catheter insertion)	Autonomic dysfunction	Hypomagnesaemia	Pericarditis
	Hypoxia	Drugs (e.g. epinephrine, TCADs)	Myocarditis
	Hypercapnia		
	Hyper/hypothyroid		
	Hypothermia		
	Vagal		
	Increased ICP		

In all cases, treatment of arrhythmias should be directed at the cause, when known. Correction of these factors alone may be sufficient to restore a normal rhythm, but in addition the efficacy of anti-arrhythmic drugs is usually enhanced if predisposing factors are treated first. For example, increased vagal tone can occur during stimulation/retraction on the peritoneum, extraocular muscles or uterine cervix. Uncontrolled sympathetic stimulation can cause tachydysrhythmias, e.g. during light anaesthesia. The management of vagal bradycardias is to release the traction/stimulation of these areas and administer a vagolytic, e.g. atropine (600 µg) or glycopyrrolate (200 µg).

Treatment of acute arrhythmias depends on clinical urgency (i.e. is the cardiac output or blood pressure compromised, or is this a precursor of a more serious dysrhythmia?). For emergency treatment of acute arrhythmias within the hospital setting, current Resuscitation Council (UK) algorithms¹ are available from www.resus.org.uk.

CVC, central venous catheter; PA, pulmonary artery catheter; TCAD, tricyclic antidepressants; ICP, intracranial pressure.

Table 2

Drug class/mechanism of action	Site of action	Vaughan-Williams	Example	Electrophysiological effects	Uses	Adverse effects
Sodium channel blockade	Conducting system	Ia	Quinidine Dysopyramide Procainamide	↑ refractory period ↑ AP duration ↑ QRS duration	SVT, VT, atrial tachyarrhythmias WPW	Arrhythmias, Torsades de pointes
	Conducting system	Ib	Lignocaine Tocainamide Mexiletine	↓ refractory period ↓ AP duration ↔ QRS duration	VF/VT during ischaemia	Hypotension, Heart block, Confusion, Seizures
	Conducting system	Ic	Flecainide Propanenone Morcizine	↔ refractory period ↔ AP duration ↑ QRS duration	Conversion / prevention of VT/VF/SVT	Arrhythmias
Beta-blockers	SAN AVN	II	Bisoprolol Atenolol	↓ automaticity	Prevention of sympathetically mediated arrhythmias	Bronchospasm, Heart block
Potassium channel blockers	Myocardium	III	Amiodarone	↑ refractory period ↑ AP duration ↔ QRS	Prevention of VT/VF/SVT	Arrhythmias Amiodarone specific: corneal deposits, deranged LFTs, Hypothyroidism
Calcium channel blockers	SAN AVN	IV	Verapamil	↓ AP duration ↓ refractory period ↓ pacemaker depolarisation	Rate control in AF Prevention of AVNRT	Heart block Hypotension
Purines	Adenosine receptors	NA	Adenosine	↓ SAN activity ↓ AVN activity ↑ e _K	Diagnosis and treatment of paroxysmal SVT	Arrhythmias Bronchospasm
Cardiac glycosides	AVN	NA	Digoxin	Enhance vagal activity Slow nodal CV Block Na ⁺ /K ⁺ -ATPase Increase calcium availability	Treatment of AF / flutter	Arrhythmias, Fatigue, Nausea, Confusion

Indications, classification and mechanisms of action of anti-arrhythmic drugs

CV = Conduction Velocity, AP = Action Potential, SAN = Sino-Atrial node, AVN = Atrioventricular Node, e_K = Potassium efflux, WPW = Wolff-Parkinson-White

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