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 (Ca²⁺) 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 Ca²⁺ channels, ATPase pumps, or opening K⁺ channels.
The resting pacemaker potential is approximately -60mV. These cells spontaneously depolarise due to a “funny current” (i_f), caused primarily by ion channels activated by hyperpolarisation that allow slow Na⁺ entry (phase 4). At a membrane potential of -50mV, transient T-type calcium channels open to permit slow Ca²⁺ influx, before a second (L-type) Ca²⁺ channel opens at the threshold potential (-40mV). Rapid entry of Ca²⁺ then causes depolarisation (phase 0). Phase 3 occurs when K⁺ channels open to allow outward movement of K⁺. These K⁺ channels close gradually during phase 4 so that reduced K⁺ efflux contributes to the depolarisation pacemaker potential.

The resting myocyte potential is -80mV. A depolarising wave propagated from the SAN causes the depolarisation. Once the threshold potential of -60mV is reached, Na⁺ channels open, causing influx and further depolarisation during phase 0. Following this, K⁺ channels open and allow efflux in phase 1. Slow Ca²⁺ channels open and allow sustained influx of Ca²⁺ in phase 2, causing mechanical contraction through the actin-myosin system. K⁺ channels open to permit efflux and repolarisation in phase 3, before hyperpolarisation in phase 4.

The SAN depolarises and this sends a wave of depolarisation across the atria. This wave pauses at the AVN, before being conducted through the His-Purkinje system to the septum and then to the ventricles.

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 Ca²⁺ influx contribute to depolarisation, whereas K⁺ efflux contributes to hyperpolarisation and reduced excitability. Ca²⁺ 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 Ca²⁺ 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 A₁ and A₂ receptors. The effect in electrically active tissue is to induce hyperpolarisation by opening K⁺ channels, which are coupled to the A₁ receptor via Gᵢ. The effect in vascular smooth muscle, elicited by A₂, is to increase cAMP through Gα. 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 β₁-adrenoreceptor blocker. This causes a reduction in the rate of depolarisation of the SAN through blocking the Gs coupled β₁-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 μg/kg/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 [Na^{+}], and decreasing [K^{+}], and so prolongation of the refractory period. The increased intracellular [Na^{+}], alters the equilibrium of the Na^{+}/Ca^{2+} exchanger; thus causing a decrease in Ca^{2+} efflux and an increase in Ca^{2+} influx, leading to an increased [Ca^{2+}]. Decreased [K^{+}], causes a slowing of atrioventricular conduction. Digoxin also enhances vagal activity causing indirect negative chronotropic effects. The vagal effects and reduced [K^{+}], slow conduction through the AV node. An additional effect is to increase [Ca^{2+}], 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 μg/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 μg/kg/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. Dronaderone 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 (Mg²⁺)**: a cofactor in many enzyme systems including the Na⁺/K⁺-ATPase. It antagonises atrial Ca²⁺ 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 Mg²⁺ levels and serum Mg²⁺ 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 veranakalant, 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

<table>
<thead>
<tr>
<th>Anatomical</th>
<th>Physiological</th>
<th>Biochemical</th>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital</td>
<td>Cardiac ischaemia</td>
<td>Hypo/hyperkalaemia</td>
<td>Sepsis</td>
</tr>
<tr>
<td>Cardiac abnormality</td>
<td>Hypotension</td>
<td>Hypocalcaemia</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Mechanical (e.g. CVC/Hickman/PA catheter insertion)</td>
<td>Autonomic dysfunction</td>
<td>Hypomagnesaemia</td>
<td>Pericarditis</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>Drugs (e.g. epinephrine, TCA)</td>
<td>Myocarditis</td>
</tr>
<tr>
<td></td>
<td>Hypercapnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyper/hypothyroid</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Hypothemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vagal</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
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<td></td>
</tr>
</tbody>
</table>

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/stimulation of the peristalsis, extraocular muscles in pethidine. Uncontrolled sympathic stimulation can cause tachyarrhythmias, 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) algorithms are available from www.resus.org.uk.

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

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


Further reading


