Drugs acting on the heart: anti-arrhythmics

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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

Royal College of Anaesthetists CPD matrix: 1A02

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

Introduction

The normal contraction of the myocardium requires organized initiation and conduction of electrical activity (Figure 1). The depolarization of the myocardium is initiated via the sino-atrial node (SAN). This pacemaker generates a depolarizing 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 synchronized 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 shows 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 depolarization promotes electrical activity, whereas potassium (K^+) efflux promotes hyperpolarization and reduces electrical activity. Therefore, anti-arrhythmic agents promote membrane stabilization by reducing these ionic movements within cells; blocking Na^+ or Ca^{2+} channels, ATPase pumps, or opening K^+ channels.

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

Which drug to use?

The first step is to diagnose the arrhythmia accurately and treat any underlying or precipitating factors (Table 1). Once the

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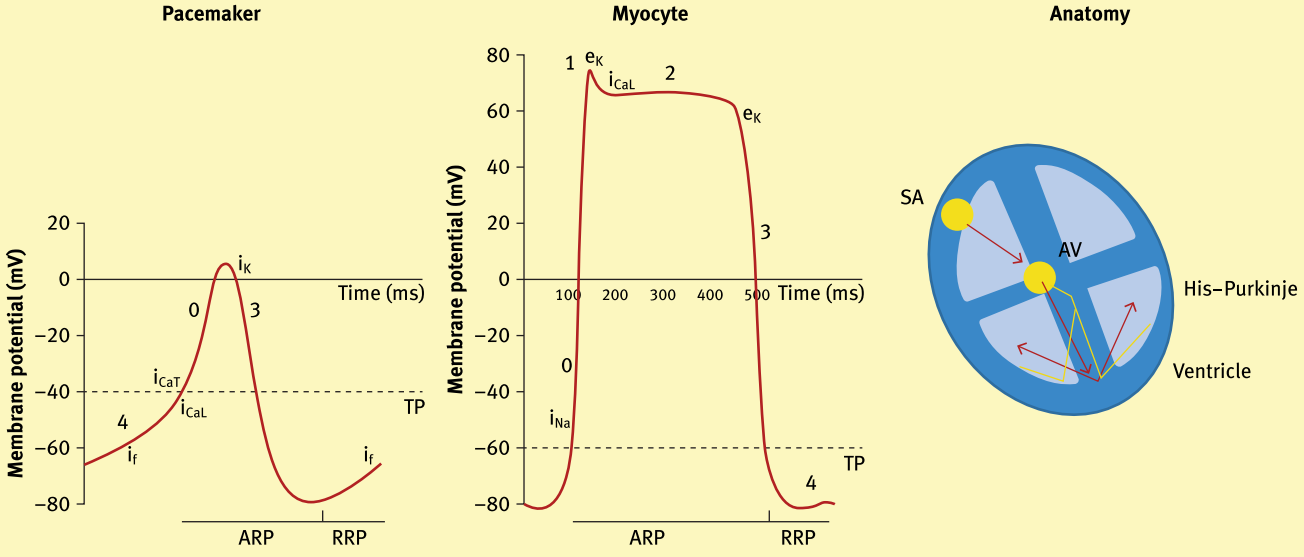
Link between myocardial electrical activity and contraction



The resting pacemaker potential is approximately −60mV. These cells spontaneously depolarize due to a 'funny current' (i_f), caused primarily by ion channels activated by hyperpolarization that allow slow Na^+ entry (phase 4). At a membrane potential of −50mV, transient T-type calcium channels open to permit slow Ca^{2+} influx, before a second (L-type) Ca^{2+} channel opens at the threshold potential (−40mV). Rapid entry of Ca^{2+} then causes depolarization (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 depolarization pacemaker potential.

The resting myocyte potential is −80mV. A depolarizing wave propagated from the SAN causes the depolarization. Once the threshold potential of −60mV is reached, Na^+ channels open, causing influx and further depolarization during phase 0. Following this, K^+ channels open and allow efflux in phase 1. Slow Ca^{2+} channels open and allow sustained influx of Ca^{2+} in phase 2, causing mechanical contraction through the actin–myosin system. K^+ channels open to permit efflux and repolarization in phase 3, before hyperpolarization in phase 4.

The SAN depolarizes and this sends a wave of depolarization 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.

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Figure 1

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 atrial fibrillatiomn (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 synchronized 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 non-pharmacological, pharmacological and electrical treatments; either to control the rate of the rhythm, or revert to sinus rhythm. Patients in AF for longer than 48 hours 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 repolarization (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 hyperpolarization 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. Hyperpolarization 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 stabilizing cardiac