# ANTI-ARRHYTHMICS DRUGS 2

**Amiodarone** is considered here as a special case, although it is usually categorised with the class III action potential prolonging antiarrhythmics in the Vaughan-Williams Classification. Amiodarone is useful in most types of arrhythmias and is considered the most efficacious of all antiarrhythmic drugs, prolonging the effective refractory period of all cardiac tissues, including the sinoatrial node, atrium, atrioventricular node, His-Purkinje system, and ventricle. This may be because it has a broad spectrum: It blocks sodium, calcium, and potassium channels and adrenoceptors. It is a benzoflu-orene derivative, is 37% iodine by weight and structurally resembles thyroxine. Amiodarone has a prolonged elimination half-time (29 days) and large volume of distribution (Vd). This drug is minimally dependent on renal excretion. The principal metabolite, desethylamiodarone, is pharmacologically active and has a longer elimination half-time than the parent drug, resulting in an accumulation of this metabolite following chronic therapy. Amiodarone causes microcrystalline deposits in the cornea and skin, thyroid dysfunction (hyper- or hypothyroidism), paresthesias, tremor, and pulmonary fibrosis. Amiodarone rarely causes new arrhythmias, perhaps because it blocks calcium channels and receptors as well as sodium and potassium channels. Because of its toxicities, amiodarone is approved for use mainly in arrhythmias that are resistant to other drugs. Nevertheless, it is used very extensively, off label, in a wide variety of arrhythmias because of its superior efficacy.

**Amiodarone**
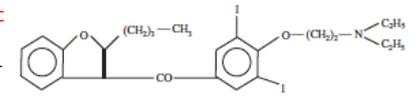
**Digoxin** All cardiac glycosides include a steroid nucleus and a lactone ring; most also have one or more sugar residues. The cardiac glycosides are often called "digitalis" because several come from the digitalis (foxglove) plant. Digoxin is the prototype agent. Inhibition of Na$^+$/K$^+$ ATPase of the cell membrane by digitalis is well documented and is considered to be the primary biochemical mechanism of action. Inhibition of Na$^+$/K$^+$ ATPase results in a small increase in intracellular sodium. The increased sodium alters the driving force for sodium-calcium exchange by the exchanger, NCX, so that less calcium is removed from the cell. The increased intracellular calcium is stored in the sarcoplasmic reticulum and upon release increases contrac-tile force. Other mechanisms of action for digitalis have been proposed, but they are probably not as important as the inhibition of ATPase. The increase in contractility evoked by digitalis results in increased ventricular ejection, decreased end-systolic and end-diastolic size, increased cardiac output, and increased renal perfusion. These beneficial effects permit a decrease in the compensatory sympathetic and renal responses previously described. The decrease in sympathetic tone is especially beneficial: reduced heart rate, preload, and afterload permit the heart to function more efficiently. Increased PR interval, caused by the decrease in atrioventricular (AV) conduction velocity, and flattening of the T wave are common electrocardiogram (ECG) effects. The effects on the atria and AV node are largely parasympathetic (mediated by the vagus nerve) and can be partially blocked by atropine. The increase in the AV nodal refractory period is particularly important when atrial flutter or fibrillation is present because the refractoriness of the AV node determines the ventricular rate in these arrhythmias. The effect of digitalis is to slow ventricular rate. Shortened QT, inversion of the T, and ST depression may occur later.
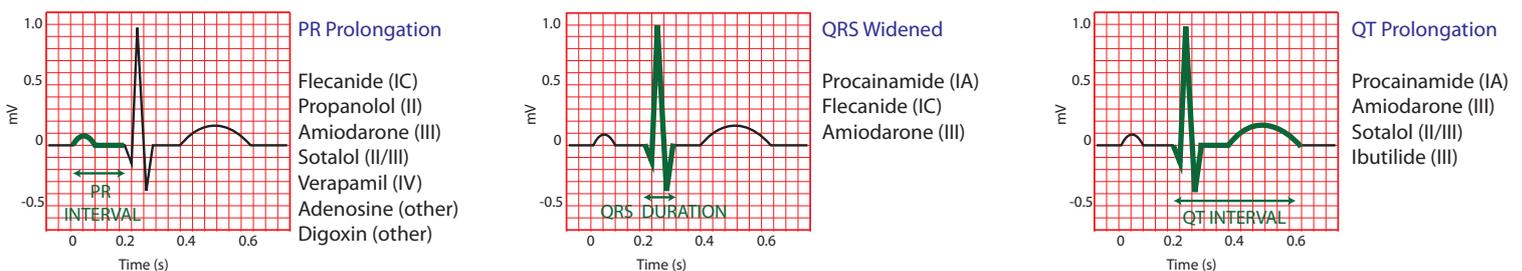
**Digoxin**
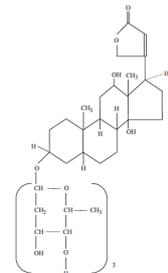
**Adenosine**
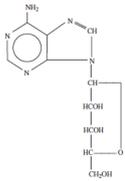
**Adenosine** is a natural purine nucleoside. It acts on the A1 adenosine receptors found in the SA and AV. When it is given in high doses (6-12 mg) as an intravenous bolus, the drug markedly slows or completely blocks conduction in the atrioventricular node, probably by hyperpolarizing this tissue (through increased $I_{K1}$) and by reducing calcium current. Adenosine is extremely effective in abolishing AV nodal arrhythmias, and because of its very low toxicity it has become the drug of choice for this arrhythmia. Adenosine has an extremely short duration of action (about 15 s). Sude effects includes flushing and hypotension, but because of their short duration these effects do not limit the use of the drug. Transient chest pain and dyspnea (probably due to bronchoconstriction) may also occur.

**Magnesium** is the fourth most common cation in the body (after Na$^+$, K$^+$ and Ca$^{2+}$), and approximately 35–40% is present in cardiac and skeletal muscle. It has an established or putative role in many physiological systems, including the inhibition of acetylcholine and noradrenaline release, and antagonism of NMDA receptors in the CNS. Magnesium ions are bound to cellular ATP, and act as a cofactor for Na+/K+ ATPase, so that intracellular concentrations of Mg$^{2+}$ may affect Na$^+$ and K$^+$ transfer. Decreased Mg$^{2+}$ concentrations may be associated with a variety of cardiac arrhythmias, and the effects observed are similar to hypokalaemia. Magnesium deficiency may facilitate Ca$^{2+}$ influx, which has a central role in cellular death during myocardial ischaemia. Magnesium salts have been used in the treatment of supraventricular arrhythmias for at least 75 years. Magnesium sulphate [20 mmol (2.5 g), given as 5 mL 50% over 20–30 min] is commonly used in ventricular tachycardia and torsade de pointes induced by antiarrhythmic agents, or to reverse arrhythmias associated with digitalis toxicity. In shock and refractory ventricular fibrillation, magnesium sulphate (8–16 mmol, i.e. 1–2 g) is sometimes given via a peripheral vein. After myocardial infarction, a bolus dose followed by an infusion of 65–72 mmol in 24 hours has been recommended. Mortality appears to be reduced, and there may be a prophylactic effect on the development of arrhythmias. However, an improvement in coronary blood flow (due to the vasodilating properties of magnesium) and a reduction in platelet aggregation may be contributory factors.

## Antiarrhythmic induced ECG changes note that class IB causes no change in the ECG

**PR Prolongation**

Flecanide (IC)
Propanolol (II)
Amiodarone (III)
Sotalol (II/III)
Verapamil (IV)
Adenosine (other)
Digoxin (other)

**QRS Widened**

Procainamide (IA)
Flecanide (IC)
Amiodarone (III)

**QT Prolongation**

Procainamide (IA)
Amiodarone (III)
Sotalol (II/III)
Ibutilide (III)

## Prodysrrhythmic effects
Most of the antiarrhythmic drugs discussed here have a narrow therapeutic window and must be used judiciously. One of the more concerning side effects in the generation of new arrhythmias. Calcium channel blockers, beta blockers and digoxin all decrease automaticity and therefore may cause sinus bradycardia. Any drug that prolongs the QT interval (usually by modifying potassium outflow) may precipitate torsades de pointes and this includes the class IA and the class III antiarrhythmics (although it is rare for amiodarone to cause this). Some drugs effectively slow conduction enough to permit a recurrent rentry circuit to occur causing and incessant ventricular tachycardia (Class IA and IC). Wide complex tachycardias may be precipitated by class IC drugs in the setting of structural heart disease.

## Summary of management
The management approach may be summarised as follows

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| 1. | Initial | Ensure patient is haemodynamically stable, if not proceed to ALS guidelines<br>Perform an ECG and correctly identify the arrhythmia |
| 2. | Assessment | Identify any precipitating factors; proarrhythmogenic drugs, electrolyte abnormalities, acid/base disturbance, hypoxia, ANS disturbance, hypothermia, structural heart disease and or recent ischaemia |
| 3. | Management | Correct or remove precipitating factors<br>Establish goals of management (this may include no treatment if there is limited indication)<br>Consider non pharmacological treatment including external defibrillation, implanted pacemaker/defib, radiofrequency ablation<br>Pharmacological therapy as indicated |
| 4. | Longer term | Monitoring is required during drug initiation<br>Reduce long term risks; stroke prevention in AF, avoidance of QT prolonging medications, management of structural heart disease |

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