Key Clinical Topics in Cardiology

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3 Antiarrhythmic medications

Key points

- Antiarrhythmic drugs are commonly used for the treatment of supraventricular and ventricular tachycardia
- Antiarrhythmic drugs have pro-arrhythmic properties and are associated with fatal arrhythmias in certain situations

Introduction

The ultimate goal of antiarrhythmic drug therapy is to restore normal rhythm and conduction. When it is not possible to revert to normal sinus rhythm, drugs may be used to prevent more serious and possibly lethal arrhythmias from occurring. Antiarrhythmic drugs are used to decrease or increase conduction velocity, alter the excitability of cardiac cells by changing the duration of the effective refractory period and suppress abnormal automaticity.

The action potential

The cardiac action potential describes the molecular basis of electrical activity within the heart's cardiomyocytes. The action potential is a sudden positive shift in the cardiomyocyte's cellular membrane potential, termed depolarisation. Depolarisation not only initiates contraction within the affected cardiomyocyte, but also initiates depolarisation of adjacent cardiomyocytes. Consequently, depolarisation tends to spread in a wave-like fashion throughout the heart as depolarised cardiomyocytes initiate depolarisation of adjacent cells.

Three basic ion channels are responsible for the cardiac action potential and explain its unique shape. Here we list the ion channels and explain how their coordinated opening and closing results in the cardiac action potential.

Fast, voltage-gated sodium channel

Opening of fast sodium channels is responsible for the initial, rapid depolarisation of the cardiomyocyte (phase 0). These sodium channels allow for a rapid influx of positive, Na^+ ions into the cells which depolarise the membrane potential with extremely quick kinetics. However, these channels also quickly close and thus eliminate the Na^+ influx soon after maximum depolarisation of +20 mV is achieved.

Variable potassium channel

Cardiomyocyte potassium channels are induced to open following rapid depolarisation and allow the exit of positively-charged K^+ from the cell which is responsible for the cell's eventual repolarisation (phase 3). However, these potassium channels initially display low potassium conductance which increases gradually. This variable conductance is partially responsible for the unique plateau phase of the cardiomyocyte action potential. The initially low potassium conductance only allows for a partial repolarisation of the membrane, making possible the plateau phase. However, as the potassium conductance builds, it overwhelms all other ion conductance and thus causes the rapid repolarisation phase.

Slow calcium channel

Cardiomyocytes uniquely possess a type of slow calcium channel known as the long, L-type calcium channel. These calcium channels are slow to open following the rapid depolarisation phase but remain open for a long time afterwards (several tenths of a second). Opening of the L-type calcium channel causes an influx of calcium into the cardiomyocyte which initiates cardiac excitation–contraction coupling. The slow

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calcium channels are most responsible for the plateau phase, because they allow a influx of positive ions over a long timescale which exactly balances the initially low efflux of potassium (phase 2). The balance between calcium influx and low potassium efflux is ultimately the basis of the sustained positive membrane potential observed in the plateau phase. Eventually, however, the slow calcium channels close and the potassium channels continue to open, resulting in the rapid repolarisation phase.

All antiarrhythmic drugs directly or indirectly alter membrane ion conductance, which in turn alters the physical characteristics of cardiac action potentials. For example, some drugs are used to block fast sodium channels. These channels determine how fast the membrane depolarises (phase 0) during an action potential. Since conduction velocity is related to how fast the membrane depolarises, sodium channel blockers reduce conduction velocity. Decreasing conduction velocity can help to abolish tachyarrhythmia caused by re-entry circuits. Other types of antiarrhythmic drugs affect the duration of action potentials, and especially the effective refractory period. By prolonging the effective refractory period, re-entry tachycardia can often be abolished. These drugs typically affect potassium channels and delay repolarisation of action potentials (phase 3). Drugs that block slow inward calcium channels are used to reduce pacemaker firing rate by slowing the rate of rise of depolarising pacemaker potentials (phase 4 depolarisation). These drugs also reduce conduction velocity at the AV node, because those cells, like SA nodal cells, depend on the inward movement of Ca^{2+} ions to depolarise.

Classification of antiarrhythmic drugs

Antiarrhythmic drugs comprise many different drug classes and have several different mechanisms of action. Furthermore, some classes and even some specific drugs within a class are effective with only certain types of arrhythmias. Therefore, attempts have been made to classify the different antiarrhythmic drugs by mechanism. Although different classification schemes have been proposed, the first scheme (Vaughan-Williams) is still the one that most physicians use.

Class I antiarrhythmic agents

Quinidine, procainamide and dispopyramide have sodium and potassium channel blocking effects and are classified as 1a.

Quinidine

This is one of the oldest antiarrhythmic agents derived from the cinchona tree bark and has antimalarial, antipyretic and antiarrhythmic effects. It is eliminated via hepatic and renal routes. The most common side effects are gastrointestinal and include: nausea, abdominal pain and diarrhoea. Allergic reactions with rash, fever, haemolytic anaemia, thrombocytopaenia and hepatitis can occur. Cinchonism refers to quinidine's central nervous system (CNS) side effects such as tinnitus, delirium, hearing and visual impairment. The most serious side effect is polymorphic ventricular tachycardia/torsade de pointes. The recurrent loss of consciousness once seen with this agent (quinidine syncope) is now believed to be due to nonsustained forms of this arrhythmia.

Procainamide

This is predominantly excreted by the kidneys, its main metabolites, N-acetyl procainamide (NAPA) is a pure potassium channel blocker and is exclusively renally excreted. Patients with impaired renal function should have the dose adjusted. Procainamide is effective in treating supraventricular and ventricular arrhythmias. In patients with wide complex tachycardia, where differentiation of supraventricular arrhythmias from ventricular arrhythmias is difficult, procainamide can be used to terminate the arrhythmia if the patient is stable. Agranulocytosis is the most serious noncardiac side effect. A lupus-like syndrome with arthralgias, myalgias, pleuritic, pericarditis (polyserositis) and rash may occur. The development of positive antinuclear antibodies is seen in 60–70% of patients. Compared with systemic lupus

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erythematosus (SLE) the brain and kidneys are spared. Discontinuation of procainamide is followed by regression of these side effects.

Disopyramide

This has three important side effects. It is vagolytic causing urinary retention, constipation and dry mouth. Pyridostigmine, an acetylcholine esterase inhibitor, can be used to reverse disopyramide's vagolytic side-effects. This agent displays negative inotropy that is used in managing patients with hypertrophic cardiomyopathy and patients with neurocardiogenic (vaso vagal) syncope. Finally, disopyramide can cause torsade de pointes.

Lidocaine and mexiletine

These are class 1b antiarrhythmic agents used only the management of ventricular tachyarrhythmias. Lidocaine can only be given intravenously and is metabolised in the liver. Dose should be adjusted in patients with liver disease and heart failure. Lidocaine toxicity manifests itself with CNS side effects; paraesthesia, confusion and seizures. Mexiletine is used orally, its side effects are CNS; tremors, confusion, blurred vision and gastrointestinal; nausea and vomiting.

Flecainide and propafenone

These are class 1c antiarrhythmic agents. They are used to treat ventricular and supraventricular tachyarrhythmia's. They are contraindicated in patients with structural heart disease due to the risk of precipitating life-threatening ventricular arrhythmias. These drugs can depress systolic function. They can suppress the sinus node in patients with sick sinus syndrome and impair AV and infranodal conduction in patients with conduction disease. Propafenone has β-adrenergic receptor blocking effect.

Class II antiarrhythmic agents

These are agents that act by blocking β-receptors. As for the other classes, it has been shown that beta-blockers can also be subdivided into two classes: β1-blockers, which selectively block the β-receptors in the heart; and β2-blockers, that do not exhibit any cardiac selectivity. By blocking the effects of catecholamines at the β1-adrenergic receptors, these drugs decrease sympathetic activity on the heart. They also decrease conduction through the AV node and prolong the refractory period. Beta-blockers reduce ischaemia and therefore arrhythmias. They reduce the incidence of ventricular fibrillation and can prevent the formation of re-entry arrhythmias. They are useful in treatment of atrial or ventricular arrhythmia related to ischaemia or catecholamines, and can prevent arrhythmias in individuals with long QT syndrome. The common side effects of beta-blockers include bronchospasm, erectile dysfunction and Raynaud's phenomenon.

Class III antiarrhythmic agents

Sotalol

This is a non-specific β-adrenergic receptor blocker with potassium channel blocking properties used in managing ventricular arrhythmias and atrial fibrillation. It is renally excreted and must be used with caution if at all in patients with impaired renal function. The most serious side effect is torsade de pointes; the corrected QT (QTc) interval must be watched carefully for excess prolongation. Due to its β-adrenoreceptor blocking effect, patients with bronchospastic disease may experience an exacerbation of their pulmonary disease.

Amiodarone

This has a wide spectrum of electrophysiological effects. Although classified as a class III agent, it displays use dependent sodium channel blockade, noncompetitive α- and β-adrenoceptor blockade and calcium channel blockade. Some of its electrophysiological effect is by reducing the conversion of T4 to T3 and increasing rT3. Amiodarone is also a vasodilator and was initially developed as an antianginal agent. Amiodarone is used in managing recurrent ventricular arrhythmias in patients with cardiovascular disease. It can also assist in maintenance of sinus rhythm in patients with atrial fibrillation undergoing cardioversion. It can be administered intravenously and orally. Amiodarone has a very long half-life (40–50 days). In order to achieve rapid

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therapeutic levels, the drug should be loaded. It is hepatically excreted with no renal excretion. While it has a wide spectrum of side effects, some lethal, it rarely causes torsade de pointes and is safely used in patients with advanced cardiovascular disease. When compared with other antiarrhythmic agents, it has been shown to be superior in reducing the recurrence of ventricular arrhythmias and atrial fibrillation. Amiodarone toxicity is influenced by the dosage employed and the duration of its use. The most serious symptom of amiodarone is pulmonary fibrosis which can be fatal in 10% of individuals treated for recurrent ventricular arrhythmias. One-third of amiodarone is iodine by weight; this may interfere with biochemical assays of thyroid function and may lead to hypothyroidism or, less often, hyperthyroidism. Amiodarone accumulates in the liver and the skin, elevation of liver enzymes of up to three-fold may be seen. A slate blue discolouration of the skin is seen in patients taking high doses of amiodarone chronically. Patients on amiodarone are advised to avoid sun exposure due to photosensitivity. While all patients receiving amiodarone will ultimately develop corneal deposits that are of negligible clinical significance, rarely optic neuritis has been reported. Optic neuritis can lead to blindness; however, a causal relationship with amiodarone therapy has not been established. Up to 25% of patients on this agent will have to discontinue it because of the development of a complication or side effect.

Class IV antiarrhythmic agents

These are agents that act by blocking calcium channels. Similar to sodium channel blockers, these agents bind preferentially during the upstroke and/or the plateau of the cardiac action potential while they unblock primarily during diastole. Calcium channel blocking agents that exhibit slow recovery from block (e.g. Class IVa agents such as verapamil and diltiazem) accumulate proportionately to heart rate. By this mechanism they can interfere with tachycardia's that involve re-entry conduction in nodal tissues. Class IVb (e.g. dihydropyridine calcium channel blocking agents) have little antiarrhythmic activity, because their dissociation rate constant from cardiac calcium channels is so short that little drug remains on the receptors by the end of diastole. These agents are negatively inotropic and can produce bradycardia and hypotension.

Further reading

Antiarrhythmic drugs-clinical use and clinical decision making: a consensus document from the European Heart Rhythm Association (EHRA) and European Society of Cardiology (ESC) Working Group on Cardiovascular Pharmacology, endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and International Society of Cardiovascular Pharmacotherapy (ISCP).
Dan GA1, Martinez-Rubio A, Agewall S, et al. Europace 2018; 20:731–732.

Related topics of interest

- Atrial fibrillation (p. 27)
- Holter monitors, event recorders and implantable loop recorders (p. 96)
- Polypharmacy (p. 179)
- Stroke and transient ischaemic attack (p. 210)
- Tachycardia – supraventricular (p. 219)
- Tachycardia – ventricular (p. 223)

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Key Clinical Topics in Cardiology is an indispensable and practical guide for clinical practice and exam revision. Written and edited by a team of experts, this book provides an authoritative and up-to-date guide to common conditions and treatments in cardiovascular medicine.

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