Class 1: Sodium Channel Blockers – Antiarrhythmic Drugs

The Vaughan-Williams classification is one of the most commonly used classifications for antiarrhythmic drugs. Class 1 consists of sodium channel blockers, which in turn is divided into 3 subgroups namely 1-A, 1-B, and 1-C. This article discusses the class 1 antiarrhythmic drugs in detail, along with a description of the salient features of the individual drugs.

Antiarrhythmic Drugs

The Vaughan-Williams classification is one of the most commonly used classifications for antiarrhythmic drugs. It is very important to classify a drug so that its possible benefit can be explored. This classification groups the drugs based on their general effect (based on the mechanism of action). The drugs are grouped into 5 classes.

Note: This is a very common USMLE topic.

Class 1 consists of sodium channel blockers, which in turn are divided into 3 subgroups namely 1-A, 1-B, and 1-C. This will be explained in detail in the mechanism of action category below.

Class 2 consists of beta-blockers, which basically reduce the heart rate, conduction and cause a reduction of sympathetic activity.
Class 3 consists of potassium channel blockers and it works by means of prolonging the repolarization phase, thereby increasing the duration of the action potential. This effectively culminates in increasing the effective refractory period.

Class 4 consists of calcium channel blockers and it works by blocking the L-type calcium channels. These channels are normally found along the conduction pathway, especially near the sinoatrial (SA) node and the atrioventricular (AV) node. By means of blocking these channels, these drugs reduce the heart rate and the speed of conduction in the heart.

Class 5 antiarrhythmic drugs are other agents that cannot be categorized into the above groups.

This article discusses the class 1 antiarrhythmic drugs in detail, along with a description of the salient features of individual drugs.

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**Drugs Affecting the Cardiac Action Potential**

*Image: “Drugs affecting the cardiac action potential.” by Architha Srinivasan. License: [CC BY-SA 4.0](https://creativecommons.org/licenses/by-sa/4.0)*

The action potential
The trajectory which the action potential follows will be dependent upon the membrane potential of the cardiac cells and it varies between different parts of the heart. **There is a normal rise followed by a fall in the action potential.**

The phase 0 represents the rapid depolarization phase. It occurs because of the influx of sodium. Phase 2 and 3 represent the repolarization phase. In both of these cases, there is the prominent efflux of potassium in addition to other ions. In Phase 2, the potential, arising by the efflux of potassium, is balanced by the influx of calcium, thus making the action potential to remain as a horizontal line.

**Mechanism of Action of Sodium Channel Blockers**

Sodium-channel blockers comprise the class 1 antiarrhythmic compounds according to the Vaughan-Williams classification scheme. These drugs bind to and block the fast sodium channels that are responsible for the rapid depolarization (phase 0) of fast-response cardiac action potentials. This type of action potential is found in non-nodal cardiomyocytes (e.g., atrial and ventricular myocytes; Purkinje tissue).

Because the slope of phase 0 depends on the activation of fast sodium-channels and the rapid entry of sodium ions into the cell, blocking these channels decreases the slope of phase 0, which also leads to a decrease in the amplitude of the action potential. In contrast, nodal tissue action potentials (SA node and AV node) do not depend on fast sodium channels for depolarization; instead, phase 0 depolarization is carried out by calcium currents. Therefore, sodium-channel blockers have no direct effect on nodal tissue, at least through the blockade of fast sodium-channels.

Therefore, blocking sodium channels reduces the velocity of action potential transmission within the heart (reduced conduction velocity; negative dromotropy). This can serve as an important mechanism for suppressing tachycardias that are caused by abnormal conduction (e.g., reentry mechanisms). By decreasing abnormal conduction, reentry mechanisms can be interrupted.

The differences between the three subgroups within the class 1 are that, besides affecting phase 0 of action potentials, sodium-channel blockers may also alter the action potential duration (APD) and effective refractory period (ERP). Because some sodium-channel blockers increase the ERP (class 1-A), while others decrease the ERP (class 1-B) or have no effect on ERP (class 1-C), the Vaughan-Williams classification recognizes these
differences as subclasses of class 1 antiarrhythmic drugs.

Effects on repolarization

The effects on ERP are not directly related to the sodium channel blockade but instead, are related to drug actions on potassium channels involved in phase 3 repolarization of action potentials. These channels regulate potassium efflux from the cell (K+ out), and therefore repolarization. The drugs in these subclasses also differ in their efficacy for reducing the slope of phase 0, with 1-C drugs having the greatest and 1-B drugs having the smallest effect on phase 0 (1-A drugs are intermediate in their effect on phase 0).

The following summarizes these differences:

**Sodium-channel blockade:**

IC > IA > IB

**Increasing ERP:**

IA > IC > IB (decreases)

Increasing or decreasing the APD and ERP can either increase or decrease arrhythmogenesis, depending on the underlying cause of the arrhythmia. Increasing the ERP, for example, can interrupt tachycardia caused by re-entry mechanisms (1-A) by prolonging the duration that normal tissue is unexcitable (its refractory period).

This can prevent re-entry currents from re-exciting the tissue, as it happens with [Wolff-Parkinson-White syndrome (WPW)](https://en.wikipedia.org/wiki/Wolff%E2%80%93Parkinson-White_syndrome), caused by an aberrant path. On the other hand, increasing the APD can precipitate ‘Torsades de pointes’, a type of ventricular tachycardia caused by after-depolarizations (abnormal depolarizations of cardiac myocytes that interrupt phase 2, phase 3, or phase 4 of the cardiac action potential in the electrical conduction system of the heart).

Effects on automaticity

By mechanisms not understood and unrelated to blocking fast sodium channels, Class 1 antiarrhythmics can suppress abnormal automaticity by decreasing the slope of phase 4, which is generated by pacemaker currents.

Indirect vagal effects

The anticholinergic effect seen with this group of drugs increases the conduction along the SA and AV pathway. Thus, in a patient with [atrial flutter](https://en.wikipedia.org/wiki/Atrial_flutter), though the ventricular rate will be reduced by their sodium blocking property, class 1 antiarrhythmics can lead to both an increase in the SA rate and AV conduction, which can offset the direct effects of the drugs on these tissues.

Although a 1-A drug may effectively decrease atrial rate during flutter, it can lead to an increase in ventricular rate because of an increase in the number of impulses conducted through the AV node (anticholinergic effect), thereby requiring concomitant treatment with a beta-blocker or calcium-channel blocker to slow the AV nodal conduction. These anticholinergic actions are most prominent at the SA and AV nodes because they are extensively innervated by vagal afferent nerves. Different drugs within the 1-A subclass differ in their anticholinergic actions.
Pros & Cons and Main Indication of Sodium Channel Blockers

All three classes of drugs are indicated for the treatment of ventricular tachyarrhythmias. In addition, class 1-C drugs are very valuable in the life-threatening supraventricular tachyarrhythmias (flecainide and propafenone). Class 1-A drugs also have an effect on atrial fibrillation, along with flutter and supraventricular tachycardia.

Adverse and Side Effects Related to Sodium Channel Blockers

The side effects are discussed in detail for individual drugs.

The increase or decrease in action potential duration and the effective refractory period can act as a double-edged sword. Both of these mechanisms prevent the re-entry circuits, but, at the same time, increase the potential for causing ‘Torsades de pointes’. The proarrhythmogenic potential is generally seen among this group of drugs.

Disopyramide

Indications

Other than the indications discussed above, important consideration needs to be made in those patients who have uncontrolled atrial fibrillation. The administration of disopyramide will cause an increase in the AV nodal conduction, thereby increasing the ventricular rate in these patients.

This effect also occurs with procainamide and quinidine. Treatment with beta-blockers, digoxin or a calcium channel blocker is required. Disopyramide is deemed safe in patients with hypertrophic cardiomyopathy and is shown to have beneficial effects.

Side effects

Disopyramide has significant cardiac toxicity, it decreases the contraction of the heart (negative inotropic effect) and has the potential to cause arrhythmia. The decrease is seen even with a dose as low as 1 mg/kg and may precipitate heart failure or aggravate it in patients with pre-existing heart failure.

A common side effect of disopyramide is related to its anticholinergic effects. This includes dryness of the mouth, hesitancy during urination, and constipation.
In conditions where the cholinergic activity is already decreased, like myasthenia gravis (in this disease antibodies are formed against acetylcholine receptors), the administration of this drug will aggravate the condition.

The other conditions in which caution needs to be exercised are acute angle-closure glaucoma and urinary retention. It causes widening of the QRS complex and prolongation of the QT interval. With disopyramide therapy, though rare, there is a risk of hypoglycemia, as disopyramide may induce inhibition of the K ATP channels.

**Monitoring available for prevention of side effects**

In order to prevent the anticholinergic effect, the monitoring of serum concentrations of mono-N-dialkyl disopyramide is required in renally deranged patients.

**Treatment of side effects**

Though a decrease in contractility is self-limiting with disopyramide, acute treatment with diuretics and an inotropic agent might be required.

The anticholinergic effect can be counteracted by means of administering physostigmine and pyridostigmine, both of which increase the cholinergic activity.

QRS complex widening and prolongation of the QT interval require discontinuation of the treatment. Intravenous magnesium, by means of stabilizing depolarization, stands as a therapy in patients requiring treatment for prolongation of QT interval.

**Procainamide**

**Side effects of procainamide**

One of the most important known side effects of procainamide is its potential to cause a lupus-like syndrome, which is especially common with chronic administration. The blood of these patients will have a positive antinuclear antibody titer (where the antibodies are essentially formed against the patient’s own nuclear elements).
The other side effects include loss of appetite, the sensation of vomiting, headache, loss of sleep, dizzy feeling, hallucination, psychosis (rare but reported), rashes which are characteristically morbilliform in nature, conditions affecting the blood vessels, such as Raynaud’s phenomenon, and vasculitis of the digital ends.

Similar to the disopyramide, there occurs a potential for prolongation of the QRS complex, QT interval, and occurrence of ventricular arrhythmia.

The drug also increases the risk of causing arrhythmias and is an arrhythmogenic agent. The most common arrhythmia, which is caused by these drugs, is a form of polymorphic ventricular tachycardia known as Torsades de pointes.

Bone marrow suppression is one of the dreaded side effects of procainamide which makes patients against the routine use of this drug.

Pancytopenia and agranulocytosis occur in this condition. The cause behind it is not well delineated and it might range from allergic to hypersensitive.

**Treatment of side effects**

The symptoms of a lupus-like syndrome occur in very few patients and, even in those patients, it is self-limiting after the treatment is stopped. Other alterations include considering alternatives like N-acetyl procainamide, which does not have lupus potential.

The occurrence of bone marrow suppression warrants immediate discontinuation of the drug.

**Quinidinide**

\[
\text{Chemical structure of Quinidinide} \text{ by Ymwang42 - Using ChemDraw11.0. License: CC0}
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Quinidinide can be used for the treatment of both types of arrhythmia, namely ventricular and atrial.

**Special indication for quinidine**

Brugada syndrome is a genetic disorder associated with the development of ventricular
arrhythmias.

These patients are characterized by their potential to suffer from sudden cardiac death, and an implantable cardioverter-defibrillator (ICD), is the gold standard for prevention.

Quinidine has shown promise in this group of patients and is a standard alternative treatment. The study that proclaims this effect is a recently published study conducted in 96 patients, with a mean follow-up of 113 months.

In a systematic review where the various antiarrhythmic drugs were evaluated for atrial fibrillation, though quinidine reduced the recurrence of atrial fibrillation, it was associated with increased mortality and it was the most proarrhythmogenic agent among the tested classes of drugs (class 1-A, 1-C and 3 were included).

**Side effects of quinidine**

As with other drugs in the class A group, quinidine is also proarrhythmogenic and has the potential to cause sudden death, thus reducing its routine use. Like disopyramide, it can also precipitate heart failure.

Bigeminy and premature ventricular tachycardia are characteristic arrhythmias caused by quinidine. Prolongation of the QT interval (this is related to a delay in repolarization) that causes the risk of ‘Torsades de pointes’ is caused by this drug (maximally).

The risk of digitalis toxicity is enhanced with quinidine administration. Other risk factors include the presence of hypokalemia. On the rapid administration of a very large dose, there is a risk of hypotension with quinidine. The reason is the direct vasodilatory property of quinidine. Quinidine is also associated with a hypoglycemic effect and immune-mediated reactions.

Quinidine toxicity is described by a characteristic term known as cinchonism. The signs and symptoms of cinchonism include blurring of vision, ringing in the ears known as tinnitus, psychosis, confusion, delirium, and headache.
Treatment of side effects

The 'Torsades de pointes' can be treated by artificially increasing the pace of the atria and the ventricles and by the intravenous administration of isoproterenol.

A method of prevention is by means of alkalization with sodium bicarbonate (basically the alkalosis enhances the recovery of sodium channels). Intravenous magnesium sulfate, as discussed above, is another alternative.

Lidocaine and Its Analogs

Indications

Lidocaine is available only in intravenous form and is indicated for ventricular tachycardia. Disopyramide and mexiletine are orally active lidocaine analogs. The patients who have myocardial ischemia in addition to arrhythmias will benefit from lidocaine and mexiletine, as these drugs have improved efficacy against the ischemic myocardium.

Side effects

Tocainide has the potential to cause pulmonary fibrosis in the lungs.

Class IC Drugs

Propafenone and Flecainide: In contrast to the protective effect seen with the class 1-B drugs in patients with myocardial infarction, class 1-C compounds carry an increased risk of death in patients with myocardial infarction (the CAST trial).

Propafenone, in addition to its sodium blocking property, also has beta-blocking and calcium channel blocking activity. Both of these cause a decrease in conduction and can precipitate or aggravate heart failure.

Flecainide has the potential to induce life-threatening ventricular tachycardia.
References


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