Class 5: Other Antiarrhythmics – Antiarrhythmic Drugs

See online here

Miscellaneous antiarrhythmic drugs are those whose mechanism of action cannot be attributed to a single class of effect. Each drug has a different class of action. These drugs are not usually the first-line treatment for many conditions; their use is limited to a few specific conditions.

Background

Antiarrhythmic drugs are grouped into 5 different classes using the **Vaughan-Williams classification system** (see table below).

Class 1	Fast sodium channel blockers. In turn, it is classified into three categories, namely:	1a: quinidine, disopyramide, procainamide (prolong repolarization) 1b: mexiletine, lidocaine, phenytoin (shorten repolarization) 1c: moricizine, flecainide, propafenone (no effect on repolarization)
Class 2	Antagonist at the beta channels – Beta-blocker	Timolol, propranolol, esmolol, metoprolol, atenolol
Class 3	Potassium channel blocker	amiodarone sotalol, ibutilide, dofetilide
Class 4	Slow calcium channel blockers	Verapamil and Diltiazem

Class 5	Miscellaneous	Digoxin, Adenosine, Magnesium sulfate, Trimagnesium dicitrate

Description of the Action Potential

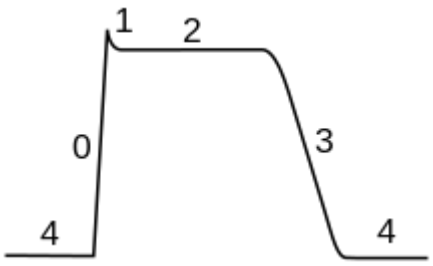

Image: “Basic cardiac action potential,” by Ksheka. License: CC BY-SA 3.0

The heart’s action potential can be divided into five phases (0 to 4), beginning and ending with phase 4. Each channel is responsible for a different phase.

Phase 4: The resting phase

- The resting potential of a cardiac muscle is negative due to a constant outward leak of K+ ions.

Phase 0: Depolarization

- Phase 0 begins with a stimulus origin. When the stimulus exceeds the threshold, it leads to depolarization.
- Fast Na+ channels open and Na+ rapidly enters the cell.
- The large Na+ current rapidly depolarizes the membrane from resting (negative) potential to 0 mV and slightly above 0 mV (positive potential)
- Fast Na+ channels then close, as they are time-dependent.
- L-type (‘long-opening’) Ca2+ channels open and cause a small, steady entry of Ca2+ into the cell.

Phase 1: Early repolarization

- Some K^+ channels open.
- An outward flow of K+ returns the positive membrane potential to approximately 0 mV.

Phase 2: The plateau phase

- L-type Ca2+ channels are still open and there is a small, constant, inward entry of Ca2+.
- At the same time, K+ moves out of the cell through its own channels.
- These 2 countercurrents are electrically balanced, and a plateau is achieved.

Phase 3: Repolarization

- Ca2+ channels are closed.
- The continuous outflow of K+ now exceeds Ca2+ entry.
- This brings the membrane potential back to resting negative potential (phase

4).

The action potential also varies between the different tissues of the heart—for example, the myocardium, conduction tissue, and impulse centers, such as sinoatrial and atrioventricular (AV) nodes.

Classification and Mechanism of Action

Miscellaneous antiarrhythmic agents include:

1. Adenosine
2. Cardiac glycosides (eg, digoxin)
3. Magnesium and potassium salts
4. Atropine

Digoxin

Digoxin is an important member of the miscellaneous group, along with adenosine.

Mechanism of action

- Digoxin is commonly used to treat two conditions:
    - Systolic heart failure
    - Supraventricular tachycardia

In the case of supraventricular tachyarrhythmia, digoxin's mechanism of action is quite different than when used in heart failure. Digoxin causes **direct suppression of conduction through the AV node**. This blockage increases the resistance for conduction of the impulse along with the AV node. An increase in vagal tone also occurs. Thus, the refractory period increases and the conduction velocity decreases.

In cases of heart failure, digoxin **inhibits the sodium/potassium ATPase pump** in the cells of the myocardium. The inhibition of the sodium/potassium ATPase leads to an increase in the sodium concentration intracellularly, which, in turn, promotes calcium influx via the sodium-calcium exchange pump. The resulting increase in intracellular calcium is the main reason why digoxin is effective in treating heart failure.

Due to its multiple side effects and narrow therapeutic index, however, other drugs are usually used for both conditions.

Digoxin toxicity

The **most dangerous** manifestation of digoxin toxicity is **an arrhythmia**. Other presentations include disturbances in the gastrointestinal tract along with neurological signs such as confusion and weakness. Changes in vision may also occur. Unfortunately, digoxin concentration does not always correlate with toxicity.

Treatment with the digoxin-specific antibody is recommended in all patients with clinically significant manifestations of digoxin toxicity. The other treatment option includes atropine, which helps decrease heart rate.

Drug interaction

The concentration of digoxin in the body increases with the administration of verapamil, quinidine, and amiodarone, as these medications can cause digoxin toxicity. As well, antacids decrease intestinal absorption and thus decrease the efficacy of digoxin.

Adenosine

Mechanism of action

Adenosine is used in the treatment of **paroxysmal supraventricular tachycardia**. It decreases conduction along with the AV node and prevents the movement of reentry circuits into the heart. The A1 receptor, along with the G0, is believed to inhibit calcium conduction, which occurs in the conduction tissue.

Adenosine is administered intravenously. Its half-life is brief (< 10 seconds).

Drug interaction

Drug efficacy is decreased by caffeine and theophylline products. Its toxic effect is enhanced by carbamazepine, digoxin, and dipyridamole.

Adverse and side effects

As with all antiarrhythmic drugs, there is always a risk of arrhythmias with adenosine administration. Other conditions that may occur include **atrial premature contraction, atrial fibrillation, and block**. Additionally, there is an increased risk of facial flushing, headache, dizziness, disturbances of the gastrointestinal tract and dyspnea, paresthesia, numbness, and discomfort in the extremities.

Magnesium and Potassium Salts

Indication and scope

In a patient with acute myocardial infarction (MI), the occurrence of hypokalemia and hypomagnesemia are risk factors for ventricular arrhythmia. The incidence of ventricular arrhythmia doubles in patients with hypokalemia. A magnesium/potassium supplement acts as a **prophylaxis to prevent the occurrence of arrhythmia** in patients with MI.

The successful correction of hypokalemia depends on the correction of hypomagnesemia. American College of Cardiology guidelines indicate that magnesium levels should be maintained above 2 mg/dl and potassium levels should be above 4 mg/ml.

Atropine

Mechanism of action

There are 2 types of cholinergic receptors: muscarinic and nicotinic. Acetylcholine, which is released from the vagal nerve ending, is responsible for deceleration of the heart, which in turn leads to bradycardia. Bradycardia is itself a significant risk factor for the occurrence of arrhythmia. Atropine acts as a **competitive antagonist of acetylcholine at the level of the muscarinic receptors**. No effect occurs in the nicotinic receptor.

Adverse and side effects

Side effects include all muscarinic receptor blocker side effects, such as dry mouth and gastrointestinal disturbances.

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Notes