Miscellaneous antiarrhythmic drugs are those whose mechanism of action cannot be attributed to a single class of effect, and every drug inside the group acts by a different class of actions. This group of drugs isn't always the first line of treatment for many conditions, and their use is limited to few specific conditions.

**Background**

The antiarrhythmic drugs are classified into five different classes by the **Vaughan-William Classification**. These are briefly highlighted in the following table:

<table>
<thead>
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<th>Class</th>
<th>Description</th>
<th>Examples</th>
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| Class 1 | Fast sodim channel blockers. In turn, it is classified into three categories, namely: | 1a — Quinidine, Disopyramide, and Procainamide (prolong repolarization)  
1b — Mexiletine, Lidocaine, and Phenytoin (shorten repolarization)  
1c — Moricizine, Flecaainde, Propafenone (no effect on repolarization) | |
| Class 2 | Antagonist at the beta channels - Beta blocker                              | Timolol, Propanolol, Esmolol, Metoprolol, and Atenolol                                         |
| Class 3 | Potassium channel blocker                                                   | Amiodarone Sotalol, Ibutilide and Dofetilde                                                    |
| Class 4 | Slow calcium channel blockers                                               | Verapamil and Diltiazem                                                                      |
Description of the Action Potential

The antiarrhythmic drugs can be better understood after gaining the knowledge of the action potential.

The action potential of the heart can be divided into five phases (from 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 and is 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 the depolarization.
- Fast Na⁺ channels open and Na⁺ rapidly enters into 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 because these are time-dependent.
- L-type (“long-opening”) Ca²⁺ channels also open and cause a small steady entry of Ca²⁺ inside 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 two 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.
- It brings the membrane potential back to resting ‘negative’ potential.
The action potential also varies between the different tissues of the heart, for instance, the myocardium, the conduction tissue, and the impulse centers, such as sinoatrial (SA) and atrioventricular (AV) nodes.

Classification and Mechanism of Action

Miscellaneous antiarrhythmic agents include:

1. Adenosine
2. Cardiac glycosides (e.g. Digoxin)
3. Magnesium and potassium salts
4. Atropine

Digoxin

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

Mechanism of action

- It is commonly used for two important conditions, namely
  - Systolic heart failure, and
  - Supraventricular tachycardia

Its mechanism of action in the case of supraventricular tachyarrhythmia is quite different when compared to that of heart failure.

Digoxin causes direct suppression of the conduction through the AV node. This blockage increases the resistance for conduction of the impulse along the AV node. There also occurs an increase in the vagal tone. Thus, the refractory period increases and the conduction velocity decrease.

In case 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 the calcium influx via the sodium-calcium exchange pump. The ultimate increase in the intracellular calcium is the main reason why digoxin is efficient in heart failure.

Due to multiple side effects and narrow therapeutic index, the usage of digoxin in both indications is superseded by the availability of better drugs.

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 the 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 the clinically significant manifestations of digoxin toxicity. The other treatment option includes atropine which helps decrease the heart rate.

Drug interaction

The concentration of digoxin in the body increases with administration of verapamil, quinidine, and amiodarone. These medications have the propensity to cause digoxin toxicity. The antacids decrease the intestinal absorption and thus cause a decrease in the
efficacy of the digoxin drug.

Adenosine

Mechanism of action

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

The half-life of adenosine is of few seconds (<10 seconds) and is given by intravenous route.

Drug interaction

Drug efficacy is decreased by caffeine and theophylline products. Its toxic effect is enhanced via additional usage of 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, as well as paresthesia, numbness, and discomfort in the extremities.

Magnesium and Potassium Salts

Indication and scope

In a patient with acute MI, the occurrence of **hypokalemia** and hypomagnesemia is a risk factor for ventricular arrhythmia. The incidence of ventricular arrhythmia increases twice in patients with hypokalemia. A magnesium & potassium supplement mainly acts as a **prophylaxis in preventing the occurrence of an arrhythmia** in patients of MI. The successful correction of hypokalemia depends on the correction of hypomagnesemia. The ACC guidelines say that the magnesium level should be maintained above 2 mg/dl and the potassium level, above the 4 mg/ml.

Atropine

Mechanism of action

There are two types of cholinergic receptors: muscarinic and nicotinic. The acetylcholine which is released from the vagal nerve ending is responsible for the 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

The side effects include all muscarinic receptor blocker side effects, such as dry mouth and gastrointestinal disturbances. They are reviewed in detail elsewhere.
References


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