Antiarrhythmic drugs

Lec1

Pharmacology 4th stage

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Class II Antiarrhythmic Drugs

- Class II agents are B-adrenergic antagonists.
- These drugs diminish Phase 4 depolarization, thus depressing automaticity, prolonging AV conduction, and decreasing heart rate and contractility
- In addition, β-blockers prevent life-threatening ventricular arrhythmias following a myocardial infarction

Class II Antiarrhythmic Drugs

- Metoprolol is the β-blocker most widely used in the treatment of cardiac arrhythmias. Compared to nonselective β-blockers, such as propranolol , it reduces the risk of bronchospasm.
- It is extensively metabolized by CYP2D6 and has CNS penetration (less than propranolol, but more than atenolol
- Common adverse effects with β-blockers include bradycardia , hypotension, and fatigue

Class III Antiarrhythmic Drugs

- Class III agents block potassium channels and, thus, diminish the outward potassium current during repolarization of cardiac cells.
- These agents prolong the duration of the action potential without altering Phase 0 of depolarization or the resting membrane potential.
- they prolong the effective refractory period. All Class III drugs have the potential to induce arrhythmias.

Amiodarone

- Amiodarone contains iodine and is related structurally to thyroxine.
- It has complex effects, showing Class I, II, III, and IV actions as well as α-blocking activity
- Despite its adverse effect profile, amiodarone is thought to be the least proarrhythmic of the class I and III antiarrhythmic drugs.

Amiodarone

- Amiodarone is effective in the treatment of severe refractory supraventricular and ventricular tachyarrhythmias .
- Despite its side-effect profile, amiodarone is the most commonly employed antiarrhythmic.
- prolonged half-life of several weeks, full clinical effects may not be achieved until months after initiation of treatment, unless loading doses are employed.
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Adverse effects

- Amiodarone shows a variety of toxic effects
- pulmonary fibrosis,
- neuropathy,
- hepatotoxicity,
- Corneal deposits, optic neuritis,
- blue-gray skin discoloration, and
- hypo- or hyperthyroidism.

- Amiodarone is subject to numerous drug interactions, since it is metabolized by CYP3A4 and serves as an inhibitor of CYP1A2, CYP2C9, CYP2D6, and P-glycoprotein.

Dronedarone

- is a benzofuran amiodarone derivative, which is less lipophilic, has lower tissue accumulation, and has a shorter serum half-life than amiodarone.
- It does not have the iodine moieties that are responsible for thyroid dysfunction associated with amiodarone.
- Currently, dronedarone is used to maintain sinus rhythm in atrial fibrillation or flutter, but it is less effective than amiodarone.

Sotalol

- Sotalol , although a class III antiarrhythmic agent, also has potent nonselective B-blocker activity.

- Sotalol blocks a rapid outward potassium current, known as the delayed rectifier. This blockade prolongs both repolarization and duration of the action potential, thus lengthening the effective refractory period.
- suppress

ectopic beats and

to reduce myocard

ial oxygen demand

Sotalol

- Sotalol is used for maintenance of sinus rhythm in patients with atrial fibrillation, atrial flutter, or refractory paroxysmal supraventricular tachycardia

- The dosing interval should be extended in patients with renal disease, since the drug is renally eliminated.

- To reduce the risk of proarrhythmic effects, sotalol should be initiated in the hospital to monitor QT interval.

Dofetilide

- Is a pure K+ channel blocker. It can be used as a first-line antiarrhythmic agent in patients with persistent atrial fibrillation and heart failure or in those with coronary artery disease.

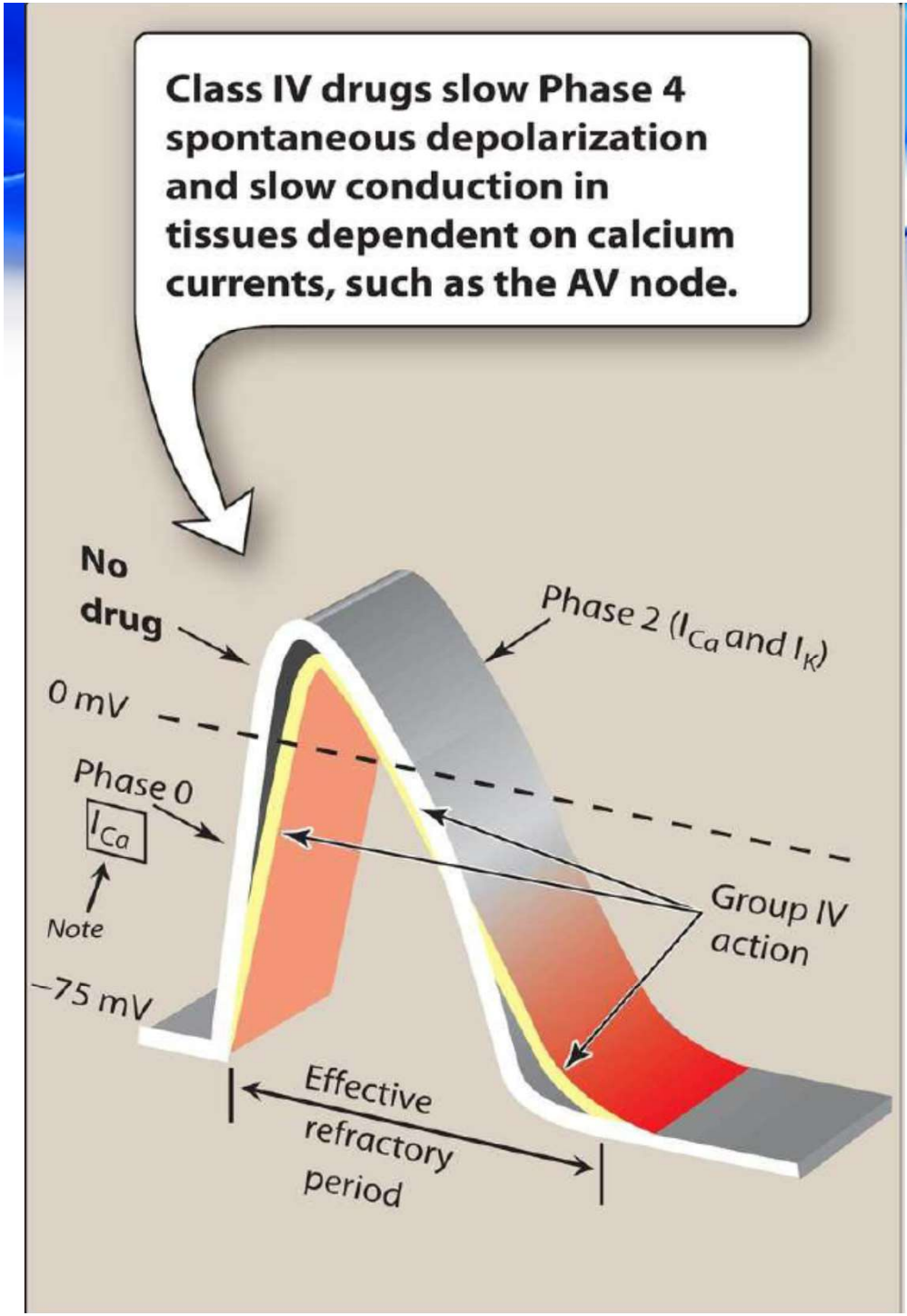
- Because of the risk of proarrhythmia, dofetilide initiation is limited to the inpatient setting.

Ibutilide

- Is a K+ channel blocker that also activates the inward Na+ current
- Ibutilide is the drug of choice for chemical conversion of atrial flutter, but electrical cardioversion has supplanted its use.
- It undergoes extensive first-pass metabolism and is not used orally.
- Initiation is also limited to the inpatient setting due to the risk of arrhythmia.

Class IV Antiarrhythmic Drugs

- The nondihydropyridine Ca2+ channel blockers verapamil and Diltiazem.
- Although voltage-sensitive Ca2+ channels occur in many different tissues, the major effect of Ca2+ channel blockers is on vascular smooth muscle and the heart.
- In the heart, verapamil and diltiazem bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by Ca2+.
- These drugs are use dependent in that they prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4
- They also slow conduction in tissues that are dependent on Ca2+ currents, such as the AV and SA nodes .


Class IV drugs slow Phase 4 spontaneous depolarization and slow conduction in tissues dependent on calcium currents, such as the AV node.
No drug
Phase 2 (I_{Ca} and I_K)
0 mV
Phase 0
I_{Ca}
Note
Group IV action
−75 mV
Effective refractory period

Class IV Antiarrhythmic Drugs

- These agents are more effective against atrial than against ventricular arrhythmias.
- They are useful in treating reentrant supraventricular tachycardia and in reducing the ventricular rate in atrial flutter and fibrillation.
- Common adverse effects include
- bradycardia,
- hypotension, and
- peripheral edema.
- Both drugs required dosage adjustments in patients with hepatic dysfunction.
- Both agents are subject to many drug interactions as they are CYP3A4 inhibitors, as well as substrates and inhibitors of P-glycoprotein.

Other Antiarrhythmic Drugs

Digoxin

- *Digoxin inhibits the Na+/K+-ATPase pump,*
- *shortening* the refractory period in atrial and ventricular myocardial cells
- prolonging the effective refractory period and diminishing velocity in the AV node.
- *Digoxin is used to control ventricular response* rate in atrial fibrillation and flutter; however, sympathetic stimulation easily overcomes the inhibitory effects of *digoxin.*
- *At toxic concentrations, digoxin causes ectopic ventricular beats that may result in VT* and fibrillation

Adenosine

- Adenosine is a naturally occurring nucleoside, but at high doses, the drug decreases conduction velocity, prolongs the refractory period, and decreases automaticity in the AV node.

- *Adenosine* has an extremely short duration of action (approximately 10 to 15 seconds) due to rapid uptake by erythrocytes and endothelial cells.

Magnesium sulfate

- Magnesium is necessary for the transport of Na+, Ca2+, and K+ across cell membranes.
- It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.
- magnesium is the drug of choice for treating the potentially fatal arrhythmia torsades de pointes and digoxin-induced arrhythmias.