Cardiovascular system

Pharmacology – Lecture 2
Antiarrhythmic Drugs / Part 2

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CLASS II ANTIARRHYTHMIC DRUGS

• Mechanism of action:

- Class II agents are β-adrenergic antagonists, or β-blockers.
- These drugs **diminish phase 4 depolarization** and, thus, **depress automaticity, prolong AV conduction, and decrease heart rate and contractility**.

• Therapeutic uses:

1. **Tachyarrhythmias** caused by increased sympathetic activity.
2. **Atrial flutter and fibrillation**
3. **AV nodal reentrant tachycardia**.
4. **Prevent** life-threatening ventricular arrhythmias following a myocardial infarction.

- In contrast to the sodium channel blockers, β-blockers and class III compounds, such as *sotalol* and *amiodarone*, are increasing in use.
- ***Metoprolol*** is the β-blocker most widely used in the treatment of cardiac arrhythmias.

• Pharmacokinetics:

1. ***Metoprolol:***

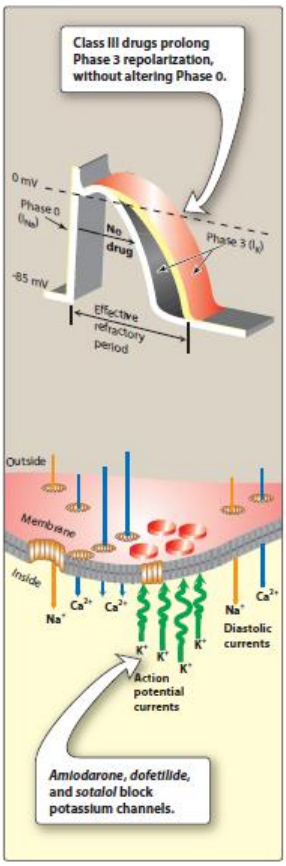
- Compared to nonselective β-blockers, such as *propranolol* , it reduces the risk of bronchospasm.
- It is extensively metabolized in the liver primarily by CYP2D6 and has CNS penetration (less than *propranolol*, but more than *atenolol*.

2. ***Esmolol:***

- Is a very-short-acting β-blocker used for intravenous administration in **acute arrhythmias** that occur during surgery or emergency situations.
- It has a fast onset of action and a short half-life, making it ideal for acute situations and also limiting its adverse effect profile.
- *Esmolol* is rapidly metabolized by esterases in red blood cells. As such, there are no pharmacokinetic drug interactions.

CLASS III ANTIARRHYTHMIC DRUGS

- Class III agents **block potassium channels** and, thus, diminish the outward potassium current during repolarization of cardiac cells.
- These agents <u>prolong the duration of the action potential</u> **without** altering phase 0 of depolarization or the resting membrane potential.
- They <u>prolong the effective refractory period</u>, increasing refractoriness.
- **All class III drugs have the potential to induce arrhythmias**.



Amiodarone

- **Mechanism of action:**
- *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.
- Its **dominant** effect is <u>prolongation of the action potential</u> duration and the <u>refractory period</u> by **blocking K+ channels**.

- **Therapeutic uses:**

- **Severe refractory supraventricular and ventricular tachyarrhythmias**.
- <u>Mainstay</u> of therapy for the rhythm management of **atrial fibrillation or flutter**.
- Despite its adverse effect profile, *amiodarone* is the <u>most commonly employed antiarrhythmic</u> and thought to be the <u>least proarrhythmic</u> of the class I and III antiarrhythmic drugs.

• Pharmacokinetics:

- *Amiodarone* is incompletely absorbed after oral administration.
- The drug is unusual in having a prolonged half-life of several weeks, and it distributes extensively in adipose tissue.
- Full clinical effects may not be achieved until months after initiation of treatment, unless **loading doses** are employed.

• Adverse effects:

- *Amiodarone* shows a variety of toxic effects, including pulmonary fibrosis, neuropathy, hepatotoxicity, corneal deposits, optic neuritis, blue-gray skin discoloration, and hypo- or hyperthyroidism.
- However, use of low doses and close monitoring reduce toxicity, while retaining clinical efficacy.
- *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

- *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*.
- Like *amiodarone*, it has class I, II, III, and IV actions.
- *Dronedarone* has a better adverse effect profile than *amiodarone* but may still cause **liver failure**.
- The drug is **contraindicated** in those with symptomatic heart failure or **permanent** atrial fibrillation due to an increased risk of death.
- 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 β-blocker activity.
- The levorotatory isomer (*l-sotalol*) has β-blocking activity, and *d-sotalol* has class III antiarrhythmic action.
- *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.
- *Sotalol* is used for maintenance of normal sinus rhythm in patients with

1. atrial fibrillation,
2. atrial flutter,
3. refractory paroxysmal supraventricular tachycardia
4. ventricular arrhythmias.

- Since *sotalol* has β-blocking properties, it is commonly used for these indications in patients with left ventricular hypertrophy or atherosclerotic heart disease.
- This drug can cause the typical adverse effects associated with β-blockers but has a low rate of adverse effects when compared to other antiarrhythmic agents.
- 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* is most often initiated in the hospital to monitor QT interval.

Dofetilide

- *Dofetilide* is a **pure** potassium 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.
- The half-life of this oral drug is 10 hours.
- The drug is mainly excreted unchanged in the urine. Drugs that inhibit active tubular secretion are contraindicated.

Ibutilide

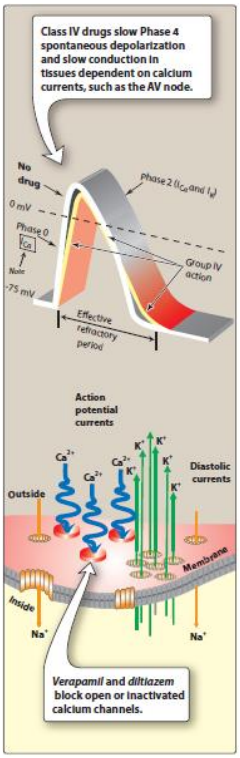
- *Ibutilide* is a potassium channel blocker that also activates the inward sodium current (mixed class III and IA action).
- *Ibutilide* is the drug of choice for chemical conversion of atrial flutter, but electrical cardioversion has supplanted its use.
- *Ibutilide* undergoes extensive first-pass metabolism and is not used orally.
- Because of the risk of QT prolongation and proarrhythmia, *ibutilide* initiation is limited to the inpatient setting.

CLASS IV ANTIARRHYTHMIC DRUGS

- Class IV drugs are the **nondihydropyridine** calcium channel blockers *verapamil* and *diltiazem*.
- Although voltage-sensitive calcium channels occur in many different tissues, the major effect of calcium channel blockers is on vascular smooth muscle and the heart.
- ***Verapamil*** shows greater action on the heart than on vascular smooth muscle, and ***diltiazem*** is intermediate in its actions.

• Mechanism of action:

- In the heart, *verapamil* and *diltiazem* bind only to open depolarized voltage-sensitive channels, thus decreasing the inward current carried by calcium.
- They prevent repolarization until the drug dissociates from the channel, resulting in a decreased rate of phase 4 spontaneous depolarization. These drugs are therefore **use-dependent**.
- They also slow conduction in tissues that are dependent on calcium currents, such as the AV and SA nodes.



• Therapeutic uses:

- These agents are more effective against atrial than against ventricular arrhythmias. They are useful in treating

1. reentrant supraventricular tachycardia
2. atrial flutter and fibrillation (in reducing the ventricular rate).

- **Pharmacokinetics:**

- Both drugs are metabolized in the liver by CYP3A4.
- Dosage adjustments may be needed in patients with hepatic dysfunction.
- Both agents are also inhibitors of CYP3A4, as well as substrates and inhibitors of P-glycoprotein. As such, they are subject to many drug interactions.

OTHER ANTIARRHYTHMIC DRUGS

Digoxin

- *Digoxin* **inhibits the Na+/K+-ATPase pump**, ultimately

1. shortening the refractory period in atrial and ventricular myocardial cells while
2. prolonging the effective refractory period and
3. diminishing conduction 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.
- Serum trough concentrations of 1.0 to 2.0 ng/mL are desirable for atrial fibrillation or flutter, whereas lower concentrations of 0.5 to 0.8 ng/mL are targeted for systolic heart failure.

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.
- Intravenous *adenosine* is the drug of choice for abolishing **acute** supraventricular tachycardia.
- It has low toxicity but causes flushing, chest pain, and hypotension.
- *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 sodium, calcium, and potassium across cell membranes.
- It slows the rate of SA node impulse formation and prolongs conduction time along the myocardial tissue.
- Intravenous *magnesium sulfate* is the salt used to treat arrhythmias, as oral *magnesium* is not effective in the setting of arrhythmia.
- Most notably, *magnesium* is the drug of choice for treating the potentially **fatal arrhythmia torsades de pointes and *digoxin*-induced arrhythmias**.

Ranolazine

- It is an antianginal drug with antiarrhythmic properties similar to *amiodarone*.
- Its main effect is to shorten repolarization and decrease the action potential duration similar to *mexiletine*.
- It is used to treat refractory atrial and ventricular arrhythmias, often in combination with other antiarrhythmic drugs.
- It is well tolerated with dizziness and constipation as the most common adverse effects.
- *Ranolazine* is extensively metabolized in the liver by CYP3A and CYP2D6 isoenzymes and is mainly excreted by the kidney. Concomitant use with strong CYP3A inducers or inhibitors is contraindicated.