PHARMACOLOGY OF ARRHYTHMIAS

Course:
Integrated Therapeutics 1

Lecturer:
Dr. E. Konorev

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Materials on:
Exam #5

Required reading:
Katzung, Chapter 14
CARDIAC ARRHYTHMIAS

• Abnormalities of the electrical rate or rhythm are known as arrhythmias

• Clinical manifestations range from benign palpitations to severe symptoms of low cardiac output, syncope, and sudden cardiac death

• Cardiac arrhythmias occur
  – In 25% of patients treated with digitalis
  – In 50% of anesthetized patients
  – In 80% of patients with acute MI

• When they should be treated
  – Some arrhythmias can precipitate serious or lethal rhythm disturbances
  – Rhythms that are too slow or too rapid that cause the reduction of cardiac output
  – Treatment of asymptomatic or minimally symptomatic arrhythmias should be avoided
ANTIARRHYTHMIC DRUGS

Divided into four classes according to mechanisms of action

• **Class 1** – Sodium channel-blocking drugs
  1A: Quinidine, Procainamide, Disopyramide
  1B: Lidocaine, Mexiletine
  1C: Flecainide, Propafenone

• **Class 2** – Beta blockers
  Acebutolol, Esmolol, Propranolol

• **Class 3** – Potassium channel-blocking drugs
  Amiodarone, Dronedarone, Sotalol, Dofetilide, Ibutilide

• **Class 4** – Cardioactive Calcium Channel Blockers
  Verapamil, Diltiazem

Miscellaneous agents
Adenosine, Magnesium, Potassium
CLASS 1A DRUGS

• Class 1A drugs
  – Block sodium channels, slow impulse conduction
  – Use-dependent block – preferentially bind to open (activated) sodium channels
    • Ectopic pacemaker cells with faster rhythms will be preferentially targeted
  – Dissociate from channel with intermediate kinetics
  – Block potassium channels
  – Prolong action potential duration and QT duration of the ECG

Effect of class 1A drugs on the action potential
CLASS 1A DRUGS

• Procainamide
  – Effective against most atrial and ventricular ectopic tachyarrhythmias, may be used in arrhythmias associated with myocardial infarction
  – Directly depresses the activities of sinoatrial and AV nodes
  – Possesses antimuscarinic activity
  – Has ganglion-blocking properties, reduces peripheral vascular resistance – may cause hypotension
  – **Pharmacokinetics**: Active metabolite N-acetylprocainamide has class 3 activity, has longer half-life, accumulates in renal dysfunction – measurements of both parent drug and metabolite are necessary
CLASS 1A DRUGS

• Procainamide
  – Adverse effects
    • Cardiac
      – QT interval prolongation
      – Induction of *torsade de pointes* arrhythmias and syncope
      – Excessive inhibition of conduction
    • Extracardiac
      – Lupus erythematosus syndrome with arthritis, pleuritis, pulmonary disease, hepatitis and fever
      – Nausea, diarrhea
      – Agranulocytosis
CLASS 1A DRUGS

• Quinidine
  – Used occasionally for the treatment of atrial flutter/fibrillation in patients with normal (but arrhythmic) hearts
  – In clinical trials patients on quinidine twice as likely have normal sinus rhythm, but the risk of death is increased two to three-fold
  – Affords antimuscarinic effect on the heart
  – Adverse effects:
    • Cardiac: QT interval prolongation, induction of torsade de pointes arrhythmia and syncope, excessive slowing of conduction throughout the heart
    • Extracardiac: GI side effects (diarrhea, nausea, vomiting), thrombocytopenia, hepatitis, fever
CLASS 1A DRUGS

• Disopyramide
  – Used for the treatment of ventricular arrhythmias
  – Affords potent antimuscarinic effect on the heart
  – Adverse effects
    • Cardiac: QT interval prolongation, induction of torsade de pointes arrhythmia and syncope, negative inotropic effect – may precipitate heart failure, excessive depression of cardiac conduction
    • Extracardiac: atropine-like symptoms – urinary retention, dry mouth, blurred vision, constipation, exacerbation of glaucoma
LONG QT SYNDROME AND TORSADE DE POINTES

Torsade de Pointes (TdP, “twisting the points”) is a rapid form of polymorphic VT associated with evidence of prolonged ventricular repolarization (long QT syndrome)

• Mechanism
  – Early afterdepolarizations due to the impaired function of K⁺ channels and delayed repolarization
  – Calcium and sodium channels return to their resting state and are reactivated because cell remains in the depolarized state

Waxing and waning pattern of the “twisting the points”
LONG QT SYNDROME AND TORSADE DE POINTEs

• One of common causes of proarrhythmia – drug-induced significant new arrhythmia or worsening of an existing arrhythmia
  – Antiarrhythmic drugs, groups 1A and 3 (except amiodarone)
  – Antipsychotics
  – Antihistamines
  – Antibiotics
  – Antidepressants

• Torsade de pointes usually associated with lightheadedness (or syncope), may result in sudden cardiac death due to VF

Torsade de pointes started as R-on-T ectopic beat
CLASS 1B DRUGS

• Class 1B drugs
  – Block sodium channels
  – Use-dependent block – bind to inactivated sodium channels
  • Preferentially bind to depolarized cells
    – Dissociate from channel with fast kinetics – no effect on conduction
    – May shorten action potential
    – More specific action on sodium channels – do not block potassium channels, do not prolong action potential or QT duration on ECG

Normal tissue

Depolarized (damaged) tissue
CLASS 1B DRUGS

• Lidocaine
  – Blocks inactivated sodium channels (use-dependence) – selectively blocks conduction in depolarized tissue, making damaged tissue completely “electrically silent”
  – Rapid kinetics results in recovery from block between AP, with no effect on cardiac conductivity in normal tissue
  – Very efficient in arrhythmias associated with acute myocardial infarction
CLASS 1B DRUGS

• Lidocaine
  – Pharmacokinetics: extensive first-pass metabolism – used only by the intravenous route
  – Adverse effects
    • The least toxic of all Class 1 drugs
    • Cardiovascular: may cause hypotension in patients with heart failure by inhibiting cardiac contractility, proarrhythmic effects are uncommon
    • Neurological effects: paresthesias, tremor, slurred speech, convulsions
CLASS 1B DRUGS

• Mexiletine
  – Orally active drug
  – Electrophysiological and antiarrhythmic effects are similar to lidocaine
  – Clinical use
    • Ventricular arrhythmias
    • To relieve chronic pain, especially the pain due to diabetic neuropathy and nerve injury
  – Adverse effects
    • Tremor
    • Blurred vision
    • Nausea
    • Lethargy
CLASS 1C DRUGS

• Class 1C drugs
  – Block sodium channels, slow impulse conduction
  – Preferentially bind to open (activated) sodium channels
  – Dissociate from channel with slow kinetics
  – Block certain potassium channels
  – Do not prolong action potential duration and QT interval duration of the ECG

Effect of class 1C drugs on action potential
CLASS 1C DRUGS

• Flecainide
  – Blocks sodium and potassium channels
  – Has no antimuscarinic effects
  – Clinical use
    • In patients with normal hearts
    • Treatment of supraventricular arrhythmias
  – Adverse effects
    • May be very effective in suppressing premature ventricular contractions, but may cause severe exacerbation of ventricular arrhythmias when administered to
      – Patients with preexisting ventricular tachyarrhythmias
      – Patients with a previous myocardial infarction
      – Patients with ventricular ectopic rhythms
CLASS 1C DRUGS

• Flecainide
  – Cardiac Arrhythmia Suppression Trial (CAST) was terminated prematurely because Flecainide and other class 1C drugs increased the mortality by 2.5-fold
**CLASS 2 DRUGS**

**Beta-blockers (Acebutolol, Propranolol, Esmolol)**

- Mechanism of action related to arrhythmias – selectively depress electrical activity of slow response cells in sinoatrial and AV nodes.
- Decrease heart rate, decrease conduction via AV node increasing PR interval duration.

**Sympathetic effect on the slow (pacemaker) cells**
- Activation of $I_f$ by cAMP.
- Increased rate of spontaneous depolarization in phase 4.
- Increased pacemaker cell activity, tachycardia, facilitation of AV conductivity.
CLASS 2 DRUGS

- Esmolol
  - Short-acting selective beta-1 blocker
  - Half-life is 10 min because of hydrolysis by blood esterases
  - Used as a continuous i.v. infusion, with rapid onset and termination of its action
  - Clinical use
    - Supraventricular arrhythmias
    - Arrhythmias associated with thyrotoxicosis
    - Myocardial ischemia or acute myocardial infarction with arrhythmias
    - As an adjunct drug in general anesthesia to control arrhythmias in perioperative period
CLASS 3 DRUGS

• Class 3 drugs
  – Block potassium channels
  – Prolong action potential duration and QT interval on ECG
  – APD prolongation is rate-dependent, with the most marked effect at slow heart rates
  – Prolong refractory period

Effect of class 3 drugs on action potential
CLASS 3 DRUGS

• Amiodarone
  – Blocks potassium channels
  – Prolongs QT interval and APD uniformly over a wide range of heart rates
  – Blocks inactivated sodium channels
  – Possesses adrenolytic activity
  – Has calcium channel blocking activities
  – Causes bradycardia and slows AV conduction
  – Causes peripheral vasodilation (effect may be related to the action of the vehicle)
  – Clinical use
    • Treatment of ventricular arrhythmias
    • Atrial fibrillation
CLASS 3 DRUGS

• Amiodarone
  – Pharmacokinetics
    • Metabolized by CYP3A4 – its half-life is affected by drugs that inhibit CYP3A4 (cimetidine), or induce it (rifampin)
    • Major metabolite is active, with very long elimination half-life (weeks-months)
    • Effects are maintained 1 to 3 months after discontinuation, and metabolites are found in the tissues 1 year after discontinuation
    • Inhibits many CYP enzymes – may affect the metabolism of many other drugs
    • All medications should be carefully reviewed in patients on amiodarone – dose adjustments may be necessary
CLASS 3 DRUGS

Amiodarone

- Adverse effects
  - **Cardiac**
    - AV block and bradycardia
    - **Incidence of torsade de pointes is low** – does not exacerbate ventricular arrhythmias
  - **Extracardiac**
    - Fatal pulmonary fibrosis
    - Hepatitis
    - Photodermatitis, deposits in the skin, gives blue-grey skin discoloration in sun-exposed areas
    - Deposits of drug in cornea and other eye tissues, optical neuritis
    - Blocks the peripheral conversion of thyroxine to triiodothyronine, also a source of inorganic iodine in the body – may cause hypo- or hyperthyroidism
CLASS 3 DRUGS

Dronedarone, a non-iodinated derivative of Amiodarone

• Action of the parent drug on thyroxine metabolism is eliminate
• Half-life is reduced to 24 h
• Possess multichannel actions (similar to Amiodarone) and $\beta$-blocking action
• Is effective in atrial fibrillation (restores sinus rhythm, decreases ventricular rate, and increases the interval between episodes of AF)

• Contraindications
  – Acute decompensated heart failure
  – Advanced chronic (class IV) heart failure
CLASS 3 DRUGS

- Sotalol
  - Class 2 (non-selective beta-blocker) and class 3 agent (prolongs APD)
  - Clinical use
    - Treatment of life-threatening ventricular arrhythmias
    - Maintenance of sinus rhythm in patients with atrial fibrillation
    - Supraventricular and ventricular arrhythmias in children
  - Adverse effects
    - Depression of cardiac function
    - Provokes torsade de pointes
CLASS 3 DRUGS

- **Dofetilide**
  - Specifically blocks rapid component of the delayed rectifier potassium current – effect is more pronounced at lower heart rates
  - Eliminated by kidneys, has very narrow therapeutic window – dose has to be adjusted based on creatinine clearance
  - Used to treat atrial fibrillation
  - Adverse effects
    - QT interval prolongation and increased risk of ventricular arrhythmias
- **Ibutilide**, a drug for IV infusion for acute conversion of atrial flutter or AF into sinus rhythm
  - Similar to Dofetilide
  - Patients require continuous monitoring after its infusion until QT interval duration returns to normal
CLASS 4 DRUGS

• Class 4 drugs
  – Block both activated and inactivated L-type calcium channels
  – Active in partially depolarized tissue and slow response cells

![Graph showing Slow Ca fluxes](image)
CLASS 4 DRUGS

- Class 4 drugs (Verapamil, Diltiazem)
  - Slow sinoatrial node depolarization, cause bradycardia
  - Prolong conduction time and refractory period in AV node
  - Suppress early and delayed afterdepolarizations
  - Antagonize slow responses in depolarized tissue
CLASS 4 DRUGS

• Verapamil, Diltiazem
  – Cause hypotension and sympathetic activation
  – Clinical use
    • Supraventricular tachycardia
    • Atrial fibrillation and flutter
  – Adverse effects
    • Cardiac
      – Negative inotropy
      – AV block
      – Sinoatrial node arrest
      – Bradyarrhythmias
    • Extracardiac
      – Constipation
      – Peripheral edema
MISCELLANEOUS AGENTS

• Adenosine
  – Activates potassium current and inhibits calcium current, causing marked hyperpolarization and suppression of action potentials in slow cells
  – Inhibits AV conduction and increases nodal refractory period
  – Used in paroxysmal supraventricular tachycardia
  – Adverse effects
    • Shortness of breath
    • Chest burning
    • AV block
    • Hypotension

• Magnesium
  – Indications
    • Digitalis-induced arrhythmias
    • Torsade de pointes
MISCELLANEOUS AGENTS

• Potassium
  – Increased extracellular potassium increases potassium conductance in the heart
  – Hyperkalemia
    • Reduces action potential duration
    • Slows conduction
    • Decreases pacemaker rate
    • Decreases ectopic pacemaker automaticity
  – Hypokalemia
    • Prolongs APD
    • Increases pacemaker rate
    • Exacerbates ectopic pacemaker arrhythmogenesis (such as torsade de pointes)
– Potassium therapy is directed towards normalizing its concentration