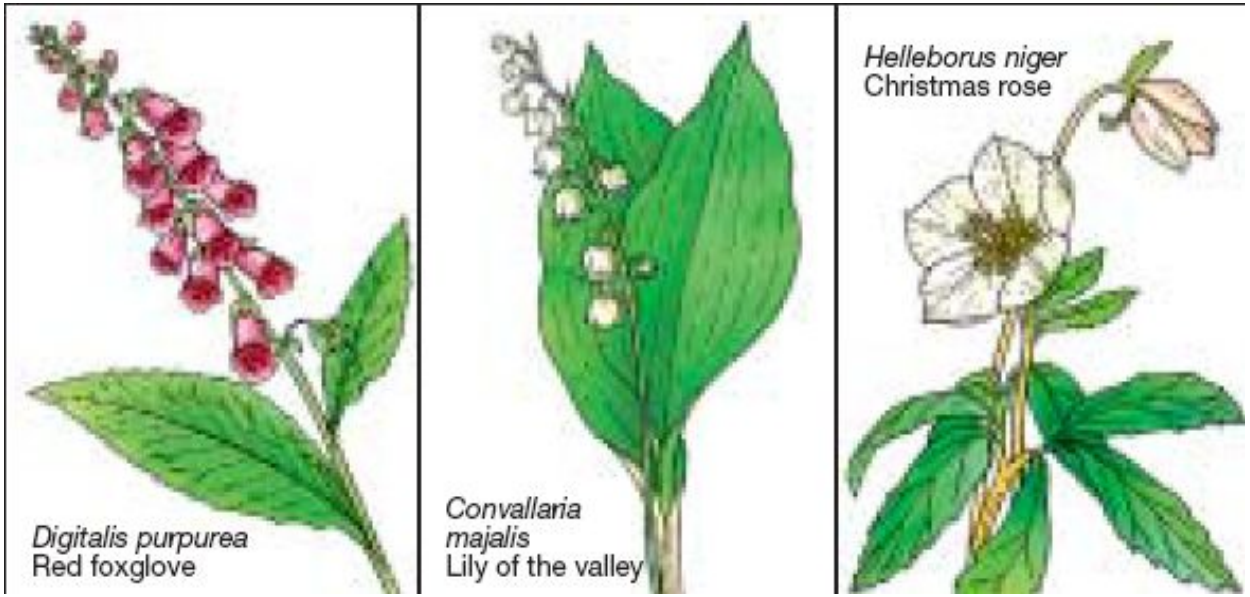
Zaporozhye State Medical University
Pharmacology and Medical Formulation Department

LECTURE № 9

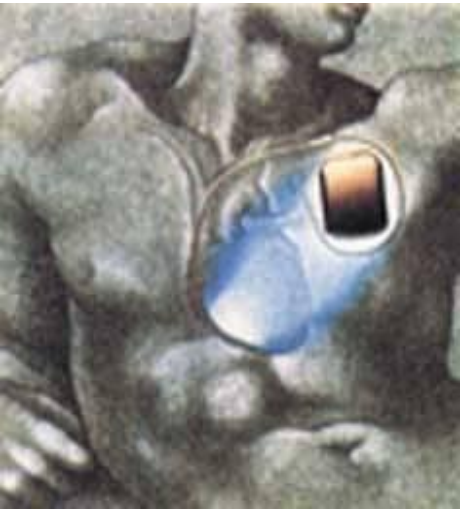
CARDIOTONIC DRUGS. ANTIARRHYTHMIC AGENTS.



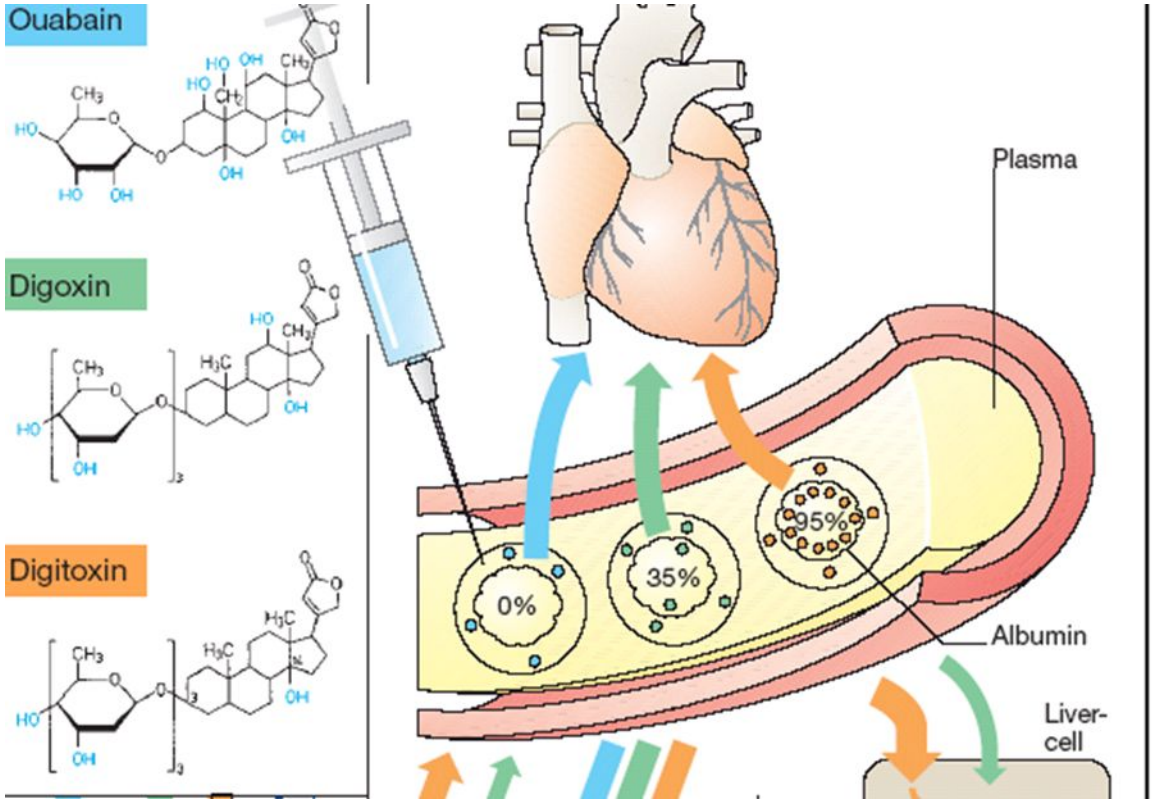
Lecturer – *Associate Professor* Irina Borisovna Samura

CARDIOTONIC DRUGS

(Cardiostimulants, or Inotropic Drugs)



1. Cardiac Glycosides
2. Agents of Non-Glycoside Structure



CARDIAC GLYCOSIDES

1. **POLAR (hydrophilic) – Strophanthin K**

Corglycone

Readily dissolve in water, do not dissolve in fat.

Poorly absorbed from the GIT, Bioavailability < 5%

Eliminate by the kidney well, binding to protein is low.

2. **NON-POLAR (lipophilic) – Digitoxine**

Readily dissolve in lipids, easily absorbed from the GIT,

Binding to protein is high

Bioavailability 95-100%.

3. **RELATIVELY POLAR**

intermediate position:

Partly hydrophilic,

Partly lipophilic –

Digoxine, Lantoside

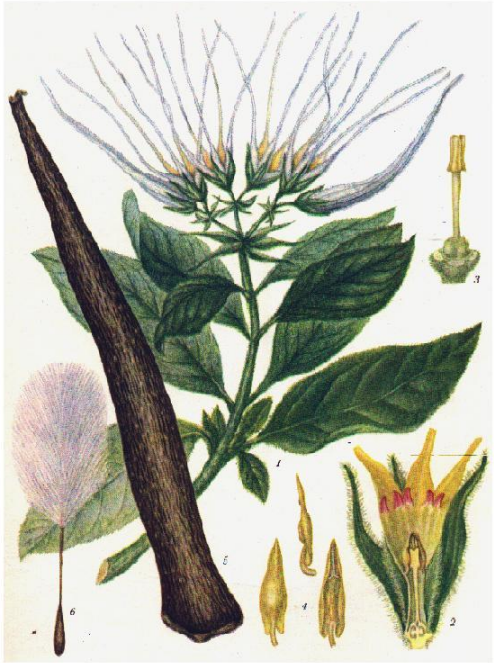
Bioavailability 35-80%.

The sources of cardiac glycosides.

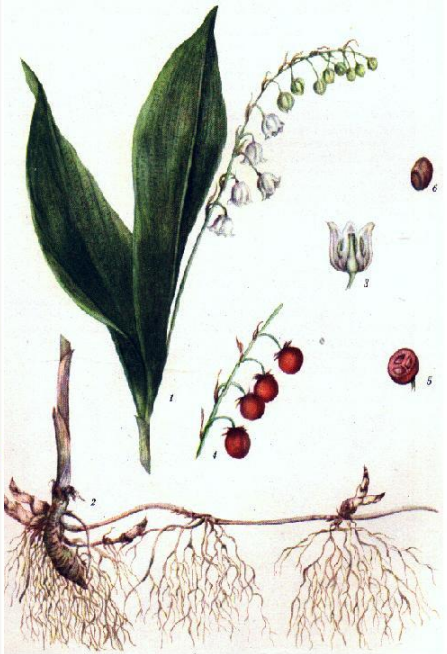
With short time of action:

- **Strophanthin-K**
- **Strophanthin-G**
- **Corglycon**
- **Adoniside**

- Absorbtion from intestine - 2-5%.
- Administration - intravenously.
- $T_{1/2}$ - 8 hours.



Strophantus gratus



Convallaria majalis

Adonis Vernalis

The sources of cardiac glycosides.

With long time of action:

Digitoxin.

- Absorbtion from intestine - 90-100%.
- Administration - perorally.
- $T_{1/2}$ - 8-9 days.

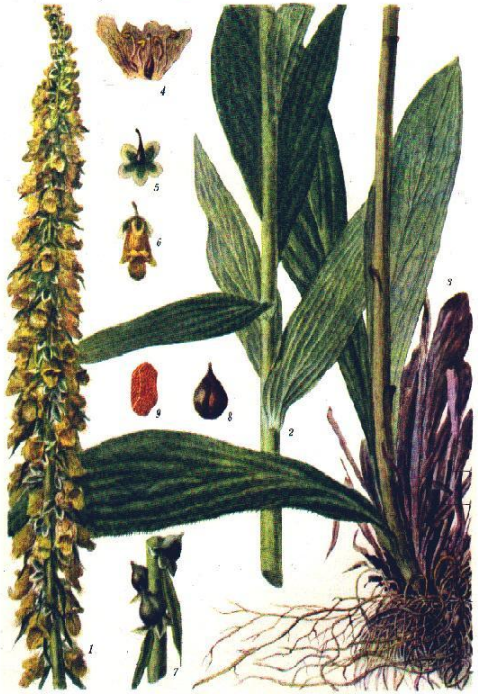
Digitalis purpurea

The sources of cardiac glycosides.

With midle time of action:

Acetyldigoxin beta, Digoxin, Methyldigoxin, Celanidum [Lantoside].

- **Absorbtion from intestine - 50-80%.**
- **Administration - perorally.**
- **$T_{1/2}$ - 34-36 hours.**

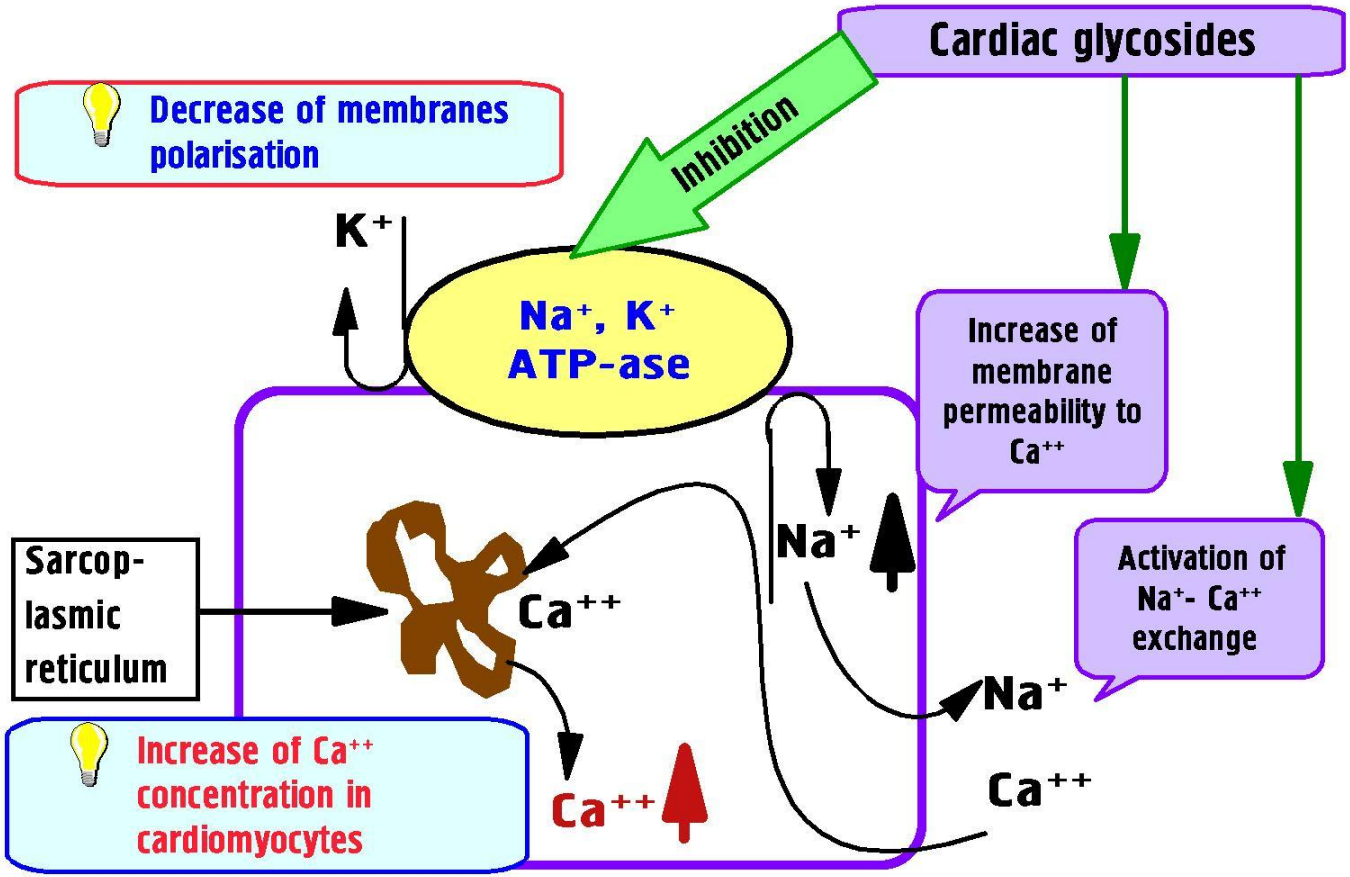


Digitalis ferruginea

Digitalis lanata

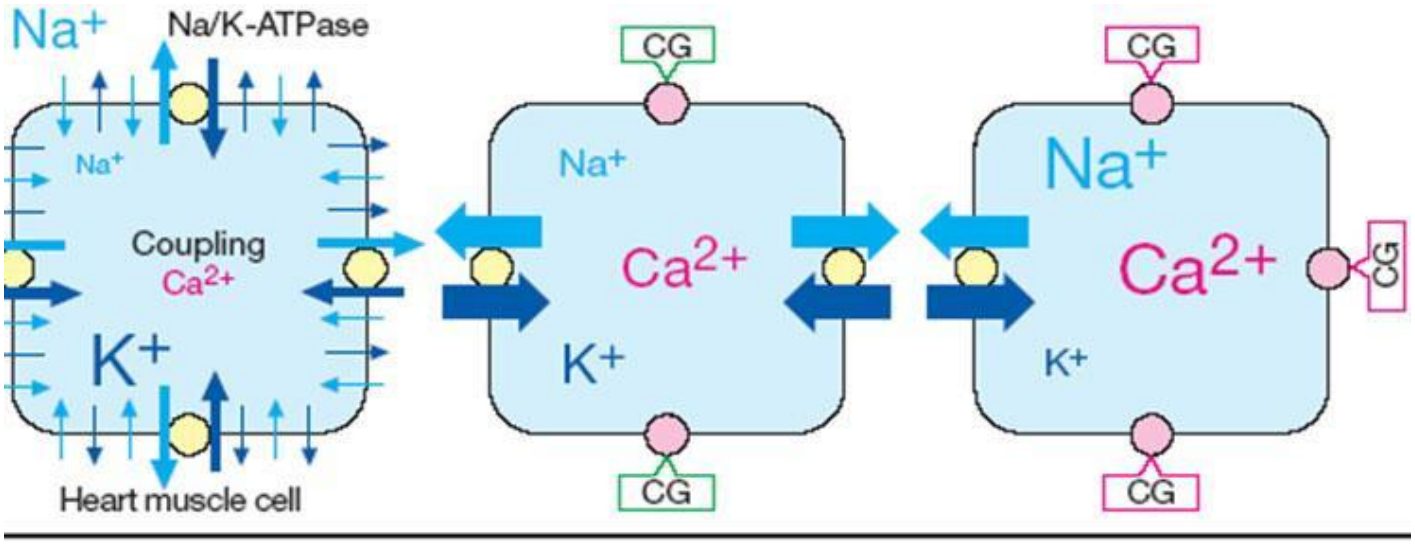
Mechanism of action of cardiac glycosides.

1. Influence upon ione balance in cardiomyocytes.



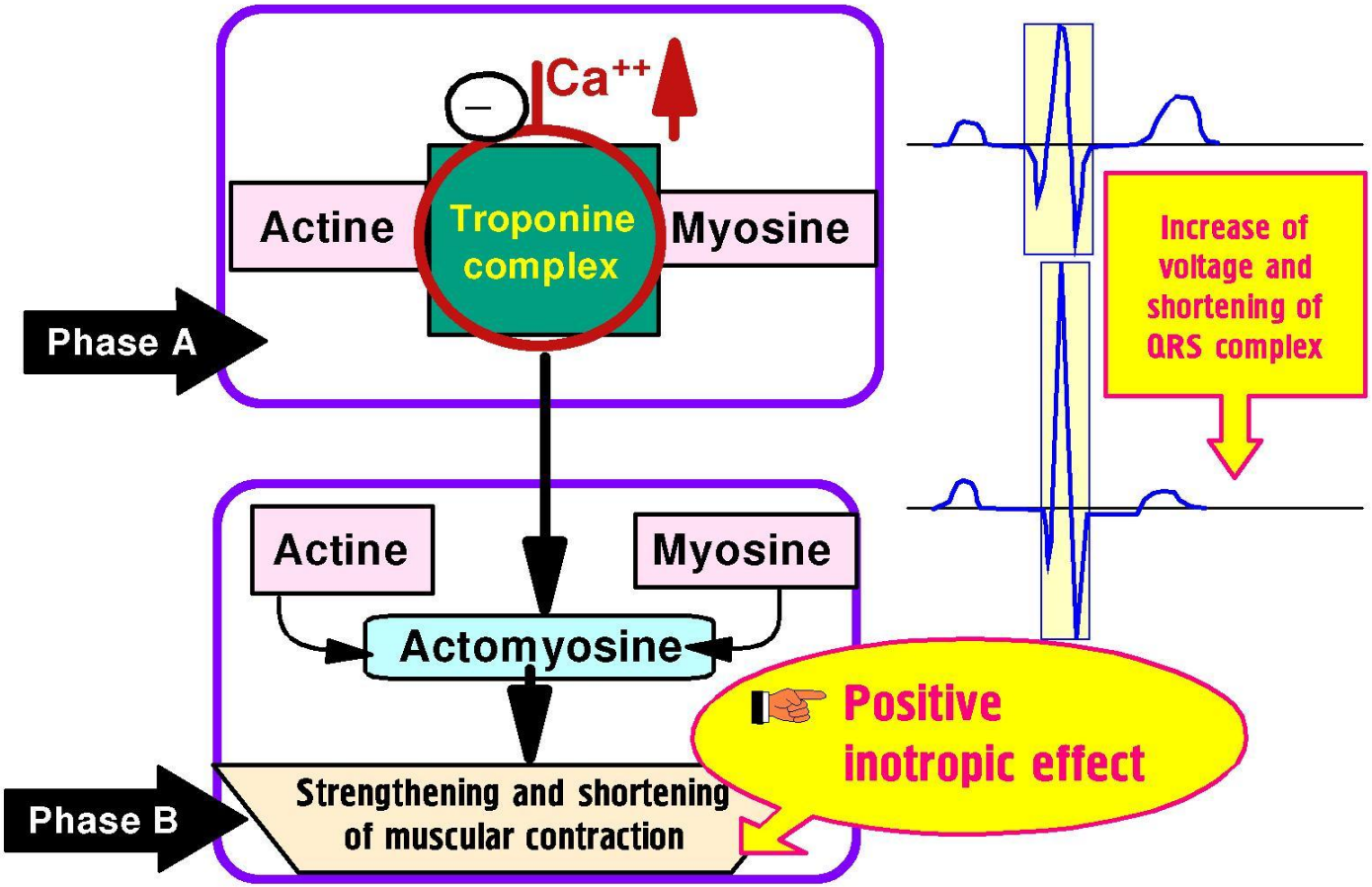
MECHANISM of ACTION of CARDIAC GLYCOSIDES

1. Na^+/K^+ ATPase inhibition =>
2. ↓ Intracellular Na^+ concentration =>
3. ↓ Ca^{2+} expulsion from the cell
   by the Na^+-Ca^+ exchanger =>
4. ↑ in Ca^{2+} concentration
5. ↓ in K^+ and Mg^{2+} concentration



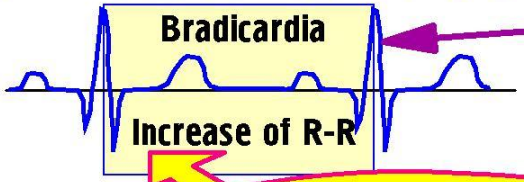
Mechanism of action of cardiac glycosides.

2. Effects as result of increasing of Ca^{++} level in cardiomyocytes.



Mechanism of action of cardiac glycosides.

3. Effects as result of positive inotropic effect.



Sinus Node

Reflex activation of Nervus Vagus centre

Exitation of mechanoreceptors

Increasie of miocardium tonus

Positive tonotropic effect

Negative chronotropic effect

Strengthening and shortening of muscular contraction (Positive inotropic effect)

Improvement of blood circulation

Going out of liquid from oedematic tissues to the blood circulation

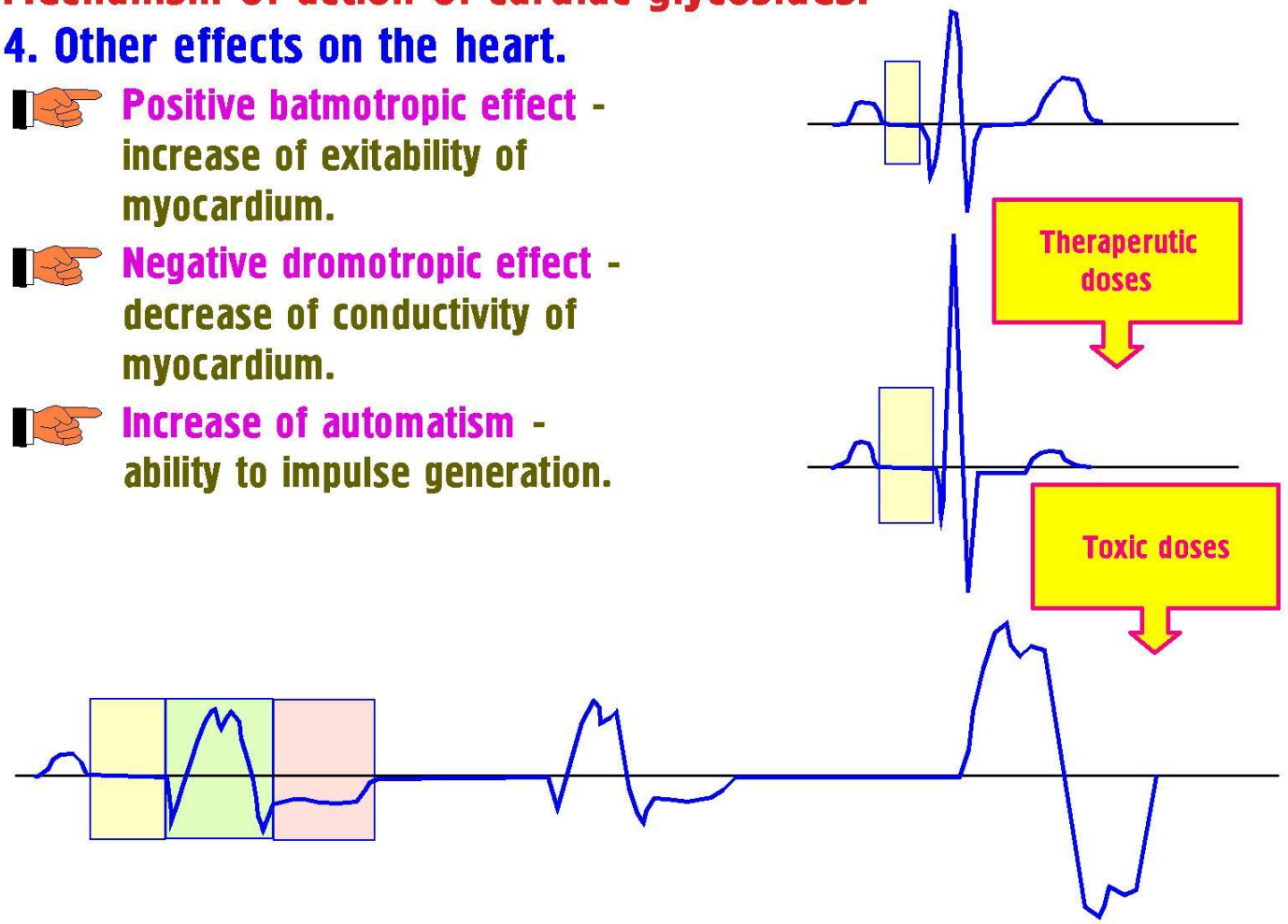
Increase of circulating blood volume and filtration pressure in kidneys

Indirect diuretic effect

Mechanism of action of cardiac glycosides.

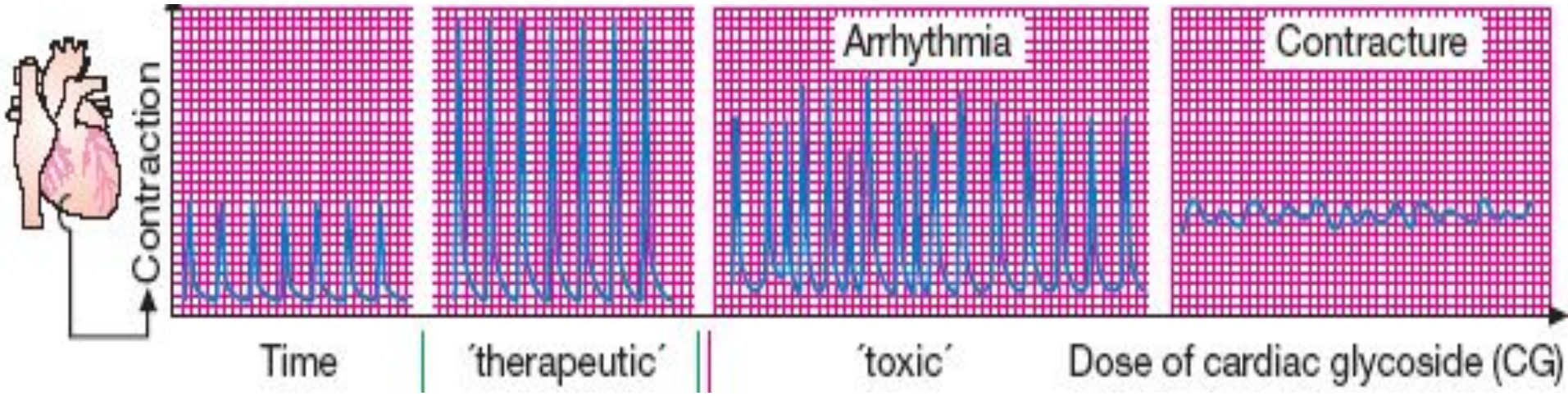
4. Other effects on the heart.

- **Positive batmotropic effect** - increase of exitability of myocardium.
- **Negative dromotropic effect** - decrease of conductivity of myocardium.
- **Increase of automatism** - ability to impulse generation.



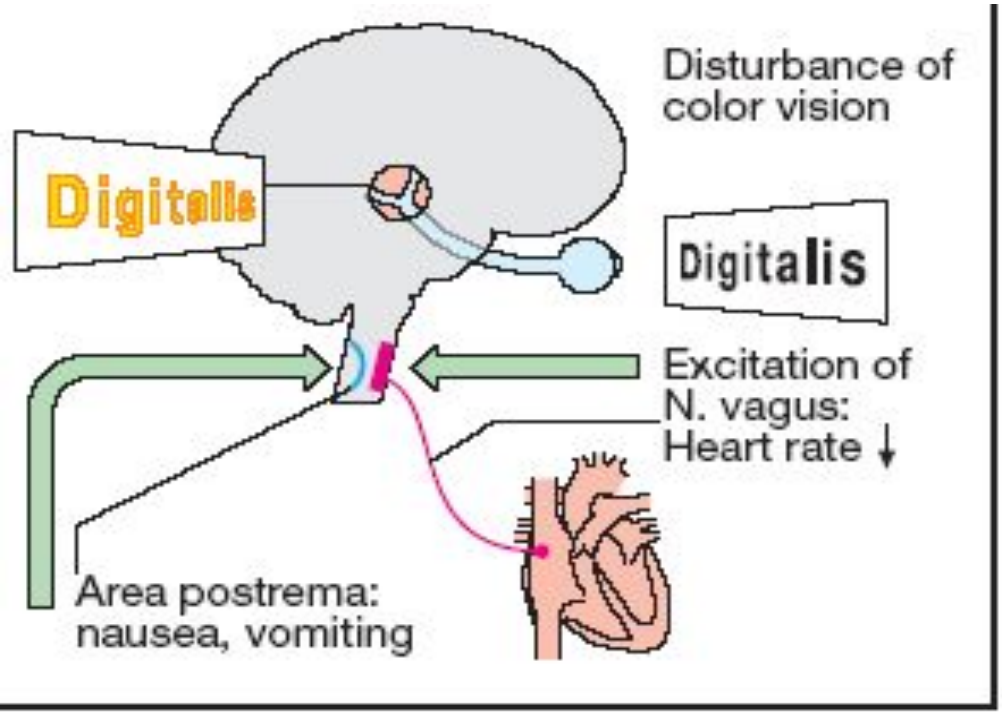
BASIC EFFECTS OF CGs ON HEART:

1. «+» **Inotropic effect:** **Force of Contraction**
2. «-» **Chronotropic effect:** **HR**
3. «-» **Dromopropic effect:** **Rate of Conduction through the AV node**
4. «+» **Batmotropic effect:**
   Myocardial Excitability

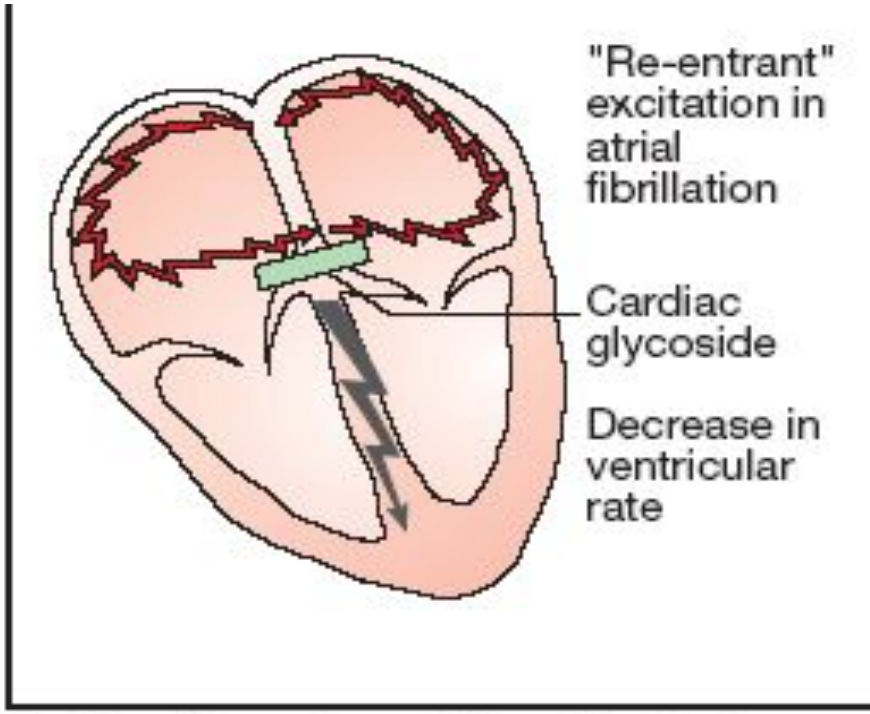


The ECG effects of CSs:

1. **P-R interval** is prolonged **(Delayed Conduction)**
2. **Q-T interval** is shortened
3. **T waves** become smaller and **inverted (negative)**



Cardiac glycoside effects on the CNS



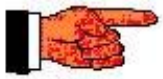
D. Cardiac glycoside effects in atrial fibrillation

CLINICAL USES of CGs:

- Acute and Chronic Heart Failure
- Pulmonary Edema
- Atrial Fibrillation and Flutter
- Paroxysmal Atrial Tachycardia

Criteria of therapeutic concentration achievement in digitalisation:

- **Weakening of heart failure symptoms**: decrease of tachicardia (till 60-80 bits/minute), dispnoe, oedemas, elemination of paleness and cyanosis, increase of diuresis etc.
- **Absence of symptoms of intoxication**.



After achievement of therapeutic concentration (3-5 days) dose of the drug must be changed to smaller dose - **supporting dose**, which is equal to quantity of drug excreted from the organism (C_{ellm}).

Symptoms of Intoxication with Cardiac Glycosides

→ **Impairment of CNS:**

- Headache, weakness, adynamia, hallucinations.
- Neuritis of vision nerve: "rings" and "balls" before eyes, xantopsia - seing of objects in yellow-green or grey-blue colors.

→ **Impairment of digestive system:**

- Nausea, vomiting, stomach-ache.

→ **Impairment of heart:**

- Increase of cardiac insufficiency.
- Bradicardia: decreasing of quantity of normal heart constrictions to less than 60 bits/minute.
- Extrasystolia, atrioventriculat blockade, ventricle fibrillation.

TREATMENT of OVERDOSE with Cardiac Glycosides

- **Discontinuation of the drug , Emesis Induction, Gastric Lavage**
- **Activated charcoal to reduce absorption in the gut**
- **Cholestiramine or Cholestipol to bind DIGITOXIN in the gut, because the drug undergoes enterohepatic recycling.**
- **K^+ - replacement doses IV , but not in patients with severe AV block.**
  Potassium Chloride (KCl - *4% solution*)
  Panangin (K^+ *Asaprginate* + Mg^{2+} *Asaprginate*)
  Asparcam (*Potassium Asaprginate + Magnesium Asaprginate*)
- **Unithiol (*Dimercaprol*):** amp. 5% solution – 5 ml IM, IV infusion
  – acts as a donator of –SH groups to restore the activity of Na+/K+ ATPase;
  – a complexing agent to bind and eliminate Ca^{2+}
- **Trilon B - a complexing agent that binds and eliminates Ca^{2+}**
- **Ventricular arrhythmias: IV Lidocaine or Phenytoin.**
- **In severe AV block, asystole and hemodynamically significant sinus bradycardia: ATROPINE restores a normal rate**
- **Specific Antibody Fragments is a treatment for life threatening drug toxicity.**

POSITIVE INOTROPIC DRUGS of NON-GLYCOSIDE STRUCTURE

1. Inhibitors of Phosphodiesterase III:

Amrinone

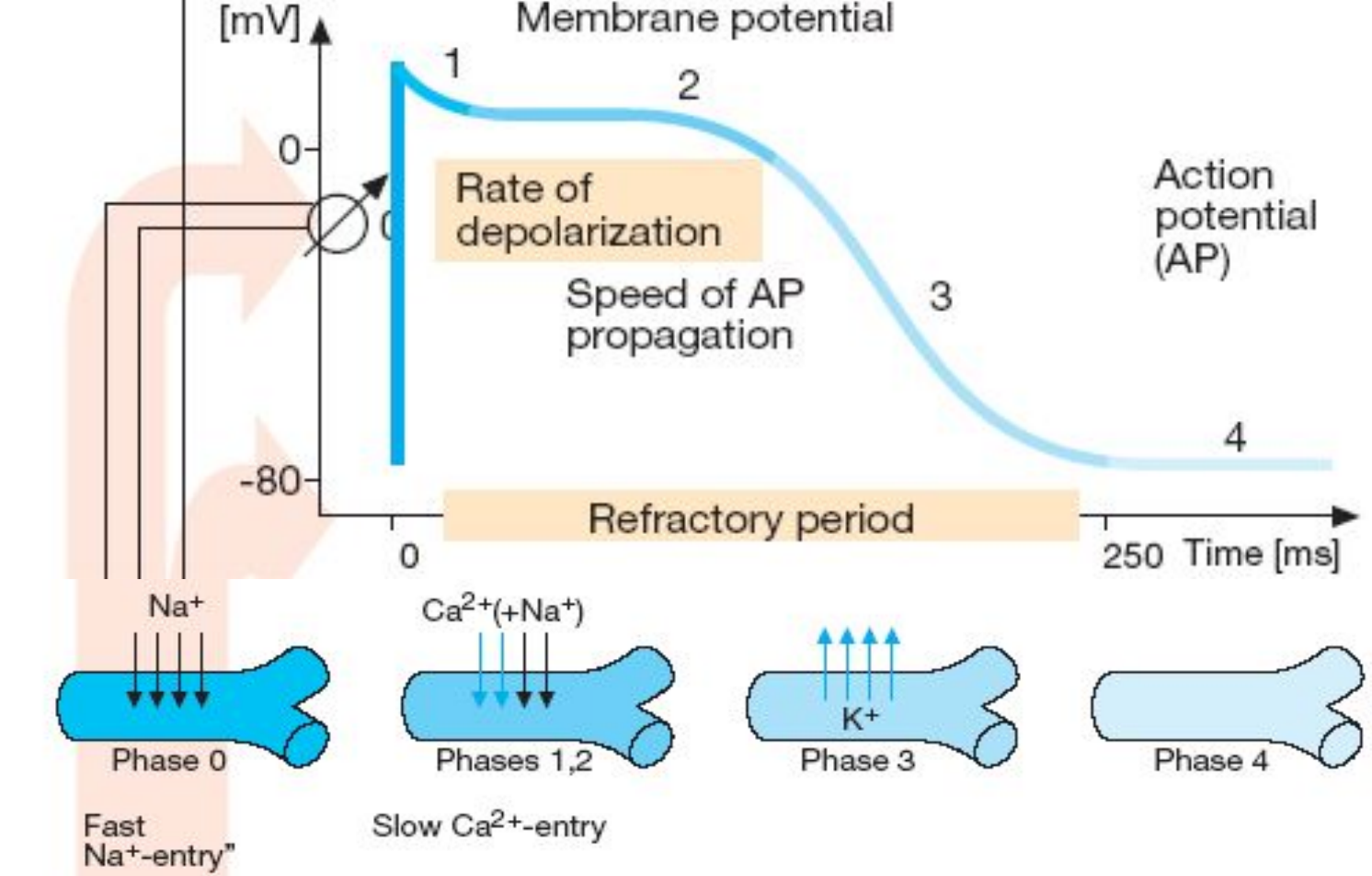
Milrinone

Vesnarinone

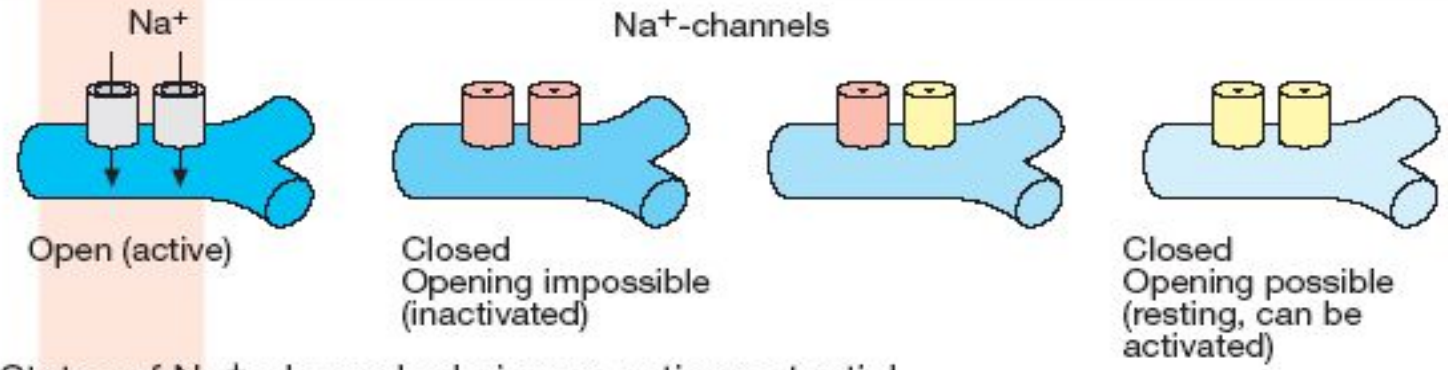
2. β_1 -Adrenomimetics:

Dobutamine

Dopamine



Ionic currents during action potential



States of Na+-channels during an action potential

Antiarrhythmic Drugs

CLASS I – Na^+ channel blockers, or Membrane-stabilizing -
Depress *Phase 0*.

Class IA: Quinidine
Novocainamide **Disopyramide**
Moderate Depression of *Phase 0* depolarization
Prolong the AP duration, have *Slow kinetics*

Class IB: Lidocaine
Mexiletine
Phenytoin (Difenin)
Depress *Phase 0* slightly,
Shorten the AP duration, have *Fast kinetics*.

Class IC: Flecainide
Ethmozin (Moracizin)
Marked Depression of *Phase 0* depolarization,
Profound slowing conduction, have *Very Slow kinetics*.

CLASS II – β-Blockers -

- **Suppress Phase 4 Depolarization:**
  - **Propronalol (*Anaprilin*)**
  - **Oxprenolol (*Trasicor*)**
  - **Nadolol (*Corgard*)**

CLASS III – K^+ Channel Blockers –

- **Amiodarone (*Cordarone*)**
- **Ornid**
- **Sotalol**

- **Prolong Phase 3 Repolarization =>**

=> □ □ *Effective Refractory period*,

CLASS IV – Ca^{++} Channel Blockers –

- **Verapamile (*Isoptine*)**
- **Dilthiazem**

- **Slow conduction and □ *Refractory period* in Ca^{2+}-dependent tissues such as the AV node**

Novocainamide (*Procainamide*) –

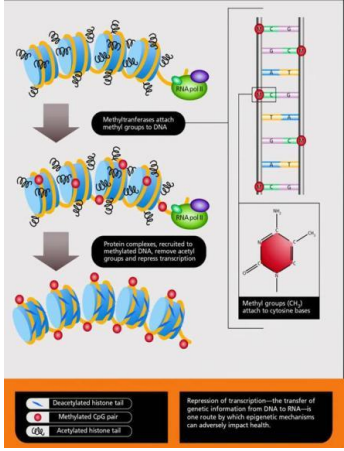
amp. 10% - 5 ml; Tab 0.25 g

interacts moderately with Na^+ channels,

⇓ Automaticity, Excitability, Conductability,

⇓ Contractility => ⇓BP

Prolongs *Refractory Period*.



Clinical uses:

Supraventricular and Ventricular Arrhythmias, Tachyarrhythmias, Fibrillation.

Adverse effects:

Hypotension, Heart Blocks, Dizziness,

Lupus Erythematosus-like *syndrome* (25-30%)

CNS effects: Depression, Hallucination, Psychosis

Lidocaine amp. 2%-10 ml, 10%-2 ml

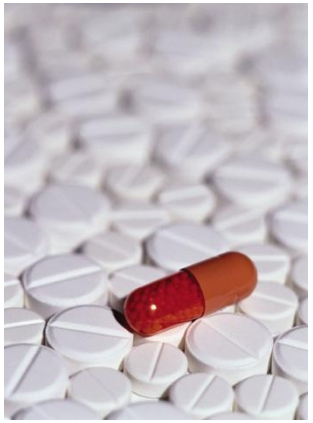
rapidly associates and dissociates from Na^+ channels.

- **Duration of** Phase 3 Repolarisation
- **Duration of the Action Potential**

Clinical Uses:

Ventricular arrhythmias including arising during Myocardial Ischemia, Acute Myocardial Infarction

CAST I and CAST II (1993-1994) –



Cardiac Arrhythmia Suppression Trial I and II

Encainide

Flecainide

Moricizine (*Ethacizine*)

successfully prevented ventricular ectopic beats in patients who had ***Myocardial Infarction*.**

However, continued therapy with either drug was associated with a 2-3-fold Death due to drug-induced Fatal Arrhythmias triggered by recurrent Myocardial Ischemia.

Amiodarone (*Kordarone*) – *Tab. 0.2 g*, amp. *5% – 3ml*

- contains 37% of iodine (1tab.– 75 mg of pure iodine)
  is related structurally to Thyroxine
  - Action Potential duration
  - Refractory period
  - has antianginal as well as antiarrhythmic activity

Clinical uses:

Severe Refractory Supraventricular and Ventricular Tachyarrhythmias and Extrasystoles

Adverse effects:

Interstitial Pulmonary Fibrosis, Hyper- or Hypothyroidism, Tremor, Ataxia, Dizziness, Liver Toxicity, Photosensitivity, Neuropathy, Muscle Weakness, Blue Skin Discoloration due to iodine accumulation in the skin.

Verapamil *- Tab 0.04, 0.08 g; amp. 0.25% - 2 ml,*

is a Ca^{2+} channel Blocker

- **Antianginal**
- **Antihypertensive**
- **Antiarrhythmic action**

⇒ **manages Stable and Unstable Angina, Prinzmetal's or Variant Angina Pectoris by ↓Afterload, both at rest and with exercise**

⇒ **↓O_2 consumption**

↓O_2 demand and cardiac work by exerting:

- **Negative Inotropic Effect**
- **↓HR**
- **Dilation of Peripheral Vessels**

Miscellaneous Antiarrhythmic Agents

- **Cardiac Glycosides:** ***Strophanthin, Digoxin***
- **Adenosine - ATP -**

is the drug of choice for **prompt conversion** of **Paroxysmal Supraventricular Tachycardia** to **sinus rhythm** – **90-95% efficacy** after introduction of **ATP** 1% water solution **1-2 ml** IV

- **Magnesium Sulphate** amp. **25% -10 ml** IV -

the best agent to treat severe Ventricular Arrhythmias – **Ventricular Tachycardia**, **Ventricular Fibrillation**

- **Potassium: KCl**

Panangin

Asparkam

AGENTS used to treat BRADYARRHYTHMIAS

1. M-Cholinoblockers: Atropine sulfate –

symptomatic bradycardia, bradyarrhythmia, supranodal and AV blockades, junctional or escape rhythm.

2. Adrenomimetics:

Adrenaline hydrochloride

Ephedrine hydrochloride

Isadrine

Dopamine

Dobutamine

3. Methylxanthines:

Theophylline, Euphylline, Theotard

4.Glucagon amp. 1 mg –

activates ***Adenylyl Cyclase*** transforming ATP into AMP.

It is used to treat overdose with β-blockers and Ca^{2+} blockers

Thank You for

Attention!