Clinical pharmacology of cardiovascular system diseases

medication: antiarrhythmic, antianginal, drugs used în cardiac failure.

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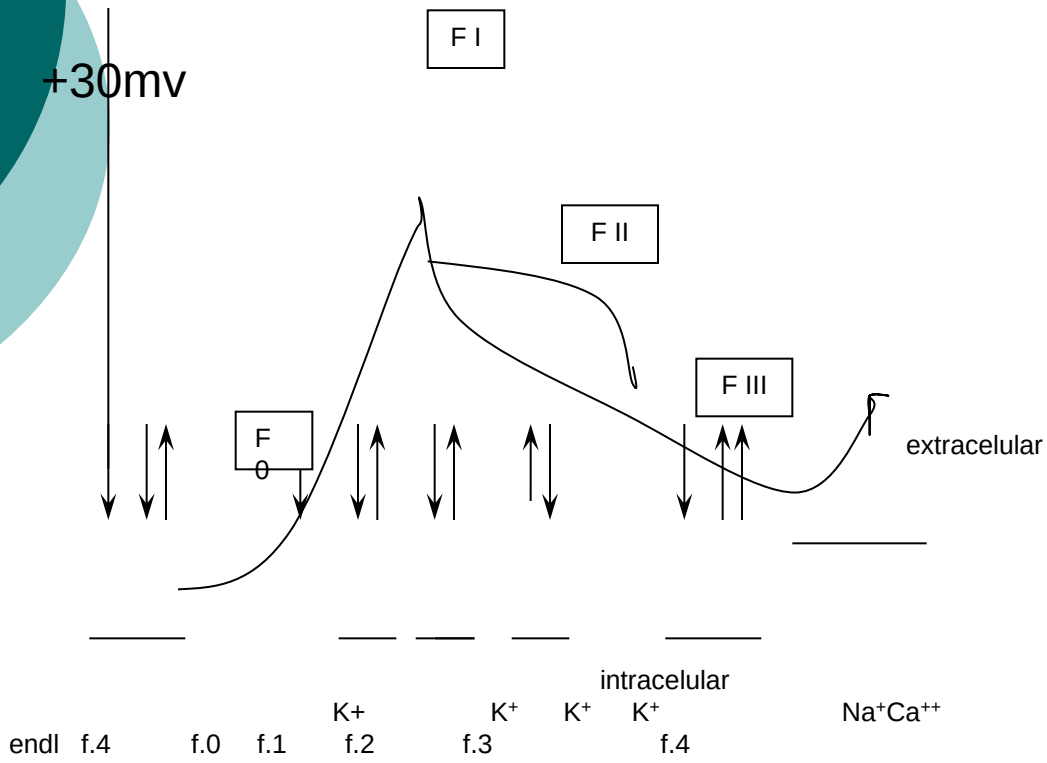
Transmembranar potential evolution (cell electrograma)



Classification of antiarrhythmic drug
(acording to Williams with modification)

Class I: Na channel blockers (and K channels to some extent)

class I A (time of restoration the Na channel blocate from 0,3 till- 1,5 sec.): **quinidine, procainamide, disopyramide, imipramine, ajmaline, lorajmaline, prajmalin**

MA: they inhibit Na+ influx (Ph 0 and 4);

Effects: - ↓ diminish the polarization;

- they prolong repolarization and ERP,
- ↓automatism, excitability, conductibility, contractility, ↑cardiac rate - adrenolitic properties (↓AP);
- parasympatholitics properties;

Indications: Useful for treatment of ventricular and atrial tachyarrhythmia

Contraindications: arrhithmias caused by digitalis, AV block, hyperpotasemia, in children.

Pharmacokinetics: Good absorbtion from intestine and binding with albumines in 90%. **T1/2-** procainamide 2-3 hours; dezopiramide 6 h, ajmaline-8 minutes. Elimination by urine.

Subclass I B (time of restoration the Na+channel blocate < 0,3 sec.): **lidocaine, tocainid, mexiletine, phenytoin**

MA: they inhibit Ca**2+** and Na+ influx (ph 4)

Eff: ↓ duration of action potential, do not influence ERP, ↓automatism; ↑cardiac rate.

Indic: ventricular arrhythmias, myocardial infarction, intoxication with digitals;

Contraind: cardiac block, liver failure, convulsion

Subclass I C (time of restoration of the blocked Na+channel > 1,5 sec): **flecainide, encainide, lorcainide, moracizine, propafenone.**

Eff: the same like IA.

Side effects: proarrhithmic effect therefore are indicated only in ventriculare tachyarrhithmia rezistent to other drugs.

Contraind: AV block, myocardial infarction.

Class II: beta-adrenoblockers:

n/selective SIA -: propranolol, nadolol, sotalol, timolol;

SIA +: pindolol, oxprenolol, alprenolol

selective SIA- : bisoprolol, esmolol, betaxolol, atenolol, metoprolol, talynolol, nebivolol*;

SIA +: acebutolol*, practolol;

They reduce sodium and calcium currents (ph 3-4);

↓automatism, excitability, conductibility, contractility, ↓cardiac rate, ↓cAMP;

Ind: supraventricular tachyarrhythmia, especially which are produsedby physical effort; WPW syndrom.

Class III: prolong refractory period

(↓K eflux (f3): amiodarone, ibutilide, dofetilide, sotalol, bretilium.

- bretylium is used as a "chemical defibrillator" when arrhythmia is resistant to standard methods.

Ind: amiodarone in supraventricular and ventricular tachyarrhythmia, WPW syndrom;

- sotalol in supraventricular tachyarrhythmia.

Class IV. Calcium channel blockers:

Verapamil, galopamil, diltiazem, bepridil

MA: block slow responses of A-V conduction (ph 2,3-4) →↑ERP

Effects: ↓automatism, excitability, conductibility, contractility,↓cardiac rate;

Highly effective in treatment of supraventricular and ventricular tachyarrhythmias.

Class V. different groups:

- **cardiac glicosides,**
- **adenozine,**
- **potasium drugs,**
- **magnezium sulfate.**

Adenosine

Is a normal component of the body, but it is given in high doses (6-12 mg) i/v, which reduces calcium current.

Bradicardia

- **-M-cholinoblockers**
- **Alfa-adrenoblockers**
- **Calcium channel blockers (dihydropiridines)**
- **Direct vasodilators**

Drugs Used in Heart Failure

Classification according to the pathogenic mecanism of action

I. Inotropic positive drugs.

II. Drugs that ↓ Preload:

III. Drugs that ↓ Afterload:

IV. Drugs that ↓ Blood volume - Diuretics.

Inotropic positive drugs.

- **Inhibitors of sodium pump** (Na+ K+-ATPase) – ***cardiac glicosides*** (strophanthin, corglicon, digoxine, digitoxine).
- **Cardiostimulators:**

  dopamino- and beta – adrenomimetics: dopamine, dobutamine, izoprenaline, dopexamine, epinephrine.
- **Phosphodiesterase inhibitors** :

  amrinone, milrinon, enoximon and

  methylxantines: aminophyilline, theophylline.
- The drugs that ↑ **heart senssitivity to calcium**- levosimendan.

II. Drugs that ↓ preload

Venodilatators: nitroglycerin, izosorbid DN and MN;

Diuretics

III. Drugs that ↓ afterload:

Arteriodilatators: hidralazine, minoxidil, diazoxid, verapamil, diltiazem, nifedipine, amlodipine, felodipine, nicardipine, nisoldipine, isradipine etc.

Drugs that ↓ preload and afterload:

Arterio- and venodilatators:

- **vasodilators:** sodium nitroprusside, bendazol, Mg_2SO_4
- Alfa-AB: prazosin, doxazosin, phentholamine,
- ACEI: captopril, enalapril, lizinopril, ramipril, quinalapril,
- ATRI: losartan, valsartan, irbesartan, etc.

Cardiac glicosides (CG)

Cardiac glicosides – of vegetal origine or semisynthetics derivates capable to intensify the contractility (force and speed contraction) of miocard in cardiac faluire with pump defficit.

- Classification of cardiac glicosides according to the:
- - speed of effect development;
- - duration of action;
- - cumulative capacity;
- - way of administration;
- - indications for administration.

I Inotrop - pozitive effect (CG)

- They ↑the force and speed of contraction → shorten the contraction duration and ventricular ejection, ↑ time of the diastolic filling, the heart empties better, pression and thelediastolic volume ↓. These all ↑ miocardic tonus, and contribute to the ↓ heart diameter and necessity in oxigen.

II. Chronotrop - negativ effect

- manifested through bradicardia and is parasimpathethic origine. Effect may be diminuated by atropine and is absent in patients with heart transplant. Clinic situation with ↑ of the simpathethic tonus and reduction of parasimpathethic (fever, thyriotoxicozes) respond slowly to chronotrop - negative action of digitalics. In this case it is necessary to associate β-adrenoblockers.

III. dromotrop - negative effect

slowness of conductivity through AV junction. Therefore action potential develops more slowly, and have more duration, refractory period became longer due to ↑ vagale influence. Dromotrop - negative effect is used in: atrial fluter, atrial fibrilation; cardiac failure with tachiarithmia, supraventricular paroxistic tachicardia.

- In AV blocade, WPW syndrom dromotrop negativ action – is unfavourable. In late AV blocade conducting is slower, that can provoke Morgan-Adams-Stokes attack. In WPW syndrom, in AV blocade, CG provoke transmission impulse through accessory ways of conductivity, producing paroxistic tachicardia.

IV. Batmotrop pozitive effect

is undesirable and provokes ectopic automatism. In atrium therapeutic dose provokes ↓duration of action potential and effective refractory period, contributes to ↑ of atrial excitement. This indirect action, is mediated by acethylcholin, explains why digitals can ↑ atrial fibrilation or fluter.

Influence on heart and haemodynamics (CG)

Normaly	**heart**	**cardiac**	**failure**
Effects	**haemodynamic modifications**	**Effects**	**haemodynamic modifications**
- Stimulate cardiac contraction; -arterioloconstric-tion; -venoconstriction systemic; -venoconstriction in liver; -Vagus stimulation.	-Do not influence cardiac output; -↑ AP; - venous retention; - Liver retention - bradicardia.	Stimulate cardiac contraction; -arteriodilatations -venodilatation; systemic; Venodilatation in liver; ↓sympathetic tonus	-↑expressively cardiac output; -↓AP; -↓systemic venous pressure; -↓ expressively of venous retention; -stoped tachicardia;

Digitalization can be achieved:

- rapidly (1-2 days) – preferable in atrial fibrilation, paroxistic tachicardia, acute pulmonary edema;
- intermediately (3-5 days)-in situation less emergency of cardiac failure;
- Slowly (5-7 days);

Plan of digitalization.

Rapidly (in acute cardiac failure).

- Strophantin i/v.
- Initial 0,125 mg in 6-10 minutes;
- After that by 0,125 mg with interval of 30-40 minutes;
- But not more than 1mg /24 hours.

Intermediate
(in subacute cardiac failure).

- Digoxin can be indicated - 3 days:
- i/v saturated dose **0,8-2,2 mg**
- Inward 1- 2,5 mg Ex:1000mcg
- I day - 50 % 40% 500mcg
- II day – 25 % 30% 250mcg+100mcg=350 /750mcg
- III day – 25% 30% 250mcg+150mcg=400/1000mcg
- 4 day- 200mcg/1000mcg

Every day 20-30 % are eliminated from body.

slow

Digoxin

- internal in I-V days by 0,125 mg- 0,75 mg/day,
  in a VI-VII days by 0,25- 0,5 mg/day.

Digitoxin

I day - 0,5 mg;

II-III day - 0,4 mg;

IV-V day - 0,3 mg;

VI-VII day –0,2 mg.

digoxin digitalization is used more often through slow parenteral and enteral method.

Efficacity and inoffensivity criteria of CG

- Manifested through:

1) Discontinuity of arithmia;
2) pulse deficit removal is considered as beneficial effect;
3) Reduced cardiac frequancy till 60-70 /minut; but bradicardia or AV blockage are considered overdoses,
4) Nocturnal tahipnoea is diminished;
5) ↑ diuresis and diminished peripheral edema and weight (not more then 0,5-1 kg/day);
6) Disappearance of the wet wheeze in lungs;
7) ↓ liver size.

ECG modifications:

1) interval PQ (not more than 0,2 sec) indicates about AV conductibility;
2) Evolution wave T shows the intensity of coronary flux.
3) Amplitude wave R and duration of the complex QRS demonstrate inotrop - pozitive effect (systolic action).

Pecularities of CG action

- In older patients are recomended smaller doses ≈ 50 % due to deficitary renal function and reduction of muscular weight,
- In children miocard is less sensible at digitalics, digoxine $T_{0,5}$ is shorter than in adults, therefore it is neccessary to administrate bigger doses (calculated on kg weight);
- premature newborn, have miocardic sensitivity more expressive and $T_{0,5}$ longer; doses must be smaller;
- diarrhoea, malabsorbtion syndrom, edematous intestinal mucosa diminish the absorbtion of CG;
- kidney failure cumulates digoxine and it is necessary to ↓ doses;

Pecularities of CG action

- hypokaliemia and hypomagneziemia are provoked by abuse of diuretics, corticosteroids and contribute to arrythmia even small doses of digitals.
- hyperkaliemia provokes digitalic blockage;
- In pacients with weight < 60 kg GC doses must be diminished by 1/4-1/3;
- in obezity the doses must not ↑ according to the weight (GC are cumulated in muscles and less in fats.

Interaction of the digoxine with other drugs

etacrinic acid	Hypokaliemie, hypomagneziemia
2. amiodarone	↑ D concentration by 69 % in blood
3. β-AB, chinidine	↑ D concentration by 100 %
4. Eritromicine	↑ D concentration by 116 %
5.Furosemide, glucoze	↑ D concentration by 60 %
6. Nifedipine	↑ D concentration by 45%
7.Sympathomimetics	Arithmia
8. Spironolactone	↓ excretion by urine
9. Tetracicline	↑ D concentration by 100 %
10. Diuretics tiazide	Toxicity, bigiminia
11.Verapamil	↑ D concentration by 41%

B. ↓ digoxin effects

The drug	Causes
1. Alcohol, antiacids	↓ GI absorbtion
2. Colestiramine	↓ GI absorbtion, ↓ $T_{1/2}$ by 50%
3. Sodium nitroprusside	↑excretion by urine
4. Metoclopramide	↓ GI absorbtion
	↓ GI absorbtion
5. Neomicine	↓ GI absorbtion
6. Prednison	↑ metabolism

Intoxication with CG

- Intoxication with CG can be manifested at 20-35% of patients.

The causes can be:

- big doses;
- association with other drugs, which increases cardiac effects (simpatomimetics, calcium);
- hypokaliemia;
- carbohydrates diet;
- treatment prolonged with saluretics and glucocorticoids;
- hypomagneziemia;
- liver failure;
- kidney failure.

Clinic Symptoms of intoxication with CG

cardio-vascular disturbance: atrial or ventricular extrasystolia, bradicardia till complete A-V blockage, ventricular fibrilation, tachiaritmia, ↓ contractility, ↓ coronary flux.

- neurological disturbance : headache, dizziness, weakness, anxiety, depression, halucination, excitement;
- oftalmics disturbance : cromatics colours perception (especially yellow or green).
- digestive disturbance : nausea, anorexia, vomiting, hypersalivation, diarrhoe, pain in abdomen.
- rarely: allergic reaction, thrombocitopenia, ginecomastia.

Treatment of intoxication.

It is recommended:

- R that ↓ CG gastrointestinal absorbtion : activated charcoal, carbosem, Medicas E, tanin, colestiramina, Mg2So4;
- R that bind CG: unitiol (contains SH group, which reactivate Na+, K+, ATP-ase);
- Specific antibodies to digoxin (digibind);
- R that bind Ca++: etilendiamintetraacetate(EDTA), sodium cytrate;
- R that ↓ hypokaliemia: potasium chlorate, panangin, asparcam;
- Abolition of arithmia: potasium drugs, fenitoin, lidocaine, propranolol, verapamil, atropine.

Antianginal drugs

- Drugs ↓ heart necesity in oxygen:

  β-adrenoblokers, bradicardics R (ivabadrine)**:**

- Drugs ↓ heart necesity O_2 **and**↑ delivery O_2 to heart:

  calcium channel blockers, potasium channel activators, nitrates, amiodarone.

- Drugs↑ delivery oxigen to heart (Coronarodilators):

  a) ***miotropics -*** *Dipiridamol,*

  b) with reflectory action - *Validol*

- Cardioprotectives **–** ***Trimetazidine, mildoniu***

Mechanism of action

- NITROGLYCERINe

- Venodilation → ↓preload → ↓ heart volume

Arteroidilation → ↓ afterload → ↓ AP

↓

↓ heart necessity in oxygen

Side effects

Earlier:

- hadeacke, weakness;
- skin congestion (more often in the upper half of the body);
- tachicardie, palpitation;
- arterial ortostatic hypotension;
- methemoglobinemia

Later *Tardive.*

- **Tolerance:**
- **initial, ↓ effect can be cauzed by activation of compensatory mecanisms of vasodilation (activation of simpato-catecholaminergic system and renin-angiotensin-aldosteron system);**
- **- later, are exhausted sulfhidril groups → ↓ metabolic forming NO and tiolnitrits;**

It can be prevented, ussing combination intermitently the nitrates retard form to provide antiischemic protection 12-16 hours, other 12 hours withouth de nitrate, ussing other remidies like β- adrenoblocker or Calcium channel blocker.

Classification CCB according to the generations

(T. Toko-Oka, W. G. Nayer, 1995, with modification)

Generation I	Generation II A	Generation II B	Generation III
Fenilalchilamins Verapamil			
Benzothiazepins Diltiazem			
Dihidropiridins Nifedipină	Nifedipină SR/ GITS Felodipină ER Nicardipină SR	Benididipină, Felodipină, Nimodipină, Nicardipină, Nisoldipină, Isradipină, Nitrendipină, Nilvadipină.	Amlodipină Lacidipină

Mecanism of action

Fenilalchilamines:

↓heart contractility and heart frequancy → ↓ heart neccesity in oxygen.

Benzothiazepines:

- ↓ heart contractility and frequancy → ↓ neccesity in oxygen;
- - artereodilation → ↓ afterload → ↓ neccesity of heart in oxigen;
- - improving coronary circulation→↑ aproving the heart with oxygen, especially the ischemical zone.

Dihydropiridines:

- arterydilation → ↓ afterload → ↓ heart neccesity in oxygen
- Improving the coronarian flux →↑heart delivery with oxygen, especially the ischemical zone.

Effects

- antihiypertensiv (hypotensive);
- cardioprotectiv, nephroprotectiv;
- antiarrythmic;
- antiplatlets;
- bronhodilator;
- antiatherogen:

- to stopd Ca2+ cumulation and lipides from arterial wall,
- decrease colagen syntheses.

Potasium channel activators as antianginals

- Opening potasium channel → ↑eflux ions K+ from cell → hyperpolarization of membrane → don't open Ca2+ dependent channell → ↓ Ca concentration intracelular → ↓muscle tonus;
- - nicorandil →↑ forming the NO → effect similar for nitrates.

Amiodarone as antianginal

- uncompetitiv blocked β1-receptors from heart →↓ heart frequancy and contractility → ↓ neccesity in oxygen;
- blocked α-receptors from vassel → ↓ afterload → ↓ necesity in oxygen;
- blocked α-receptors from coronary vessel → ↑ coronary flux →↑ heart delivery in oxygen;
- antianginal effect is manifested throught decreasing the number of anginal acces and ↑ tolerance to fizical loading.

Commonly used combinations of antianginal drugs

Rational: to diminish dosages of individual agents to reduce side effects, while keeping therapeutic effectiveness;

- b.Beta-blocker plus nitrate against exertional angina: interruption of sympathetic reflexes that compensate for vasodilation, reduced blood pressure, and lower cardiac output
- c.Nifedipine and beta-adrenergic blocker
- d.Nitrates and calcium channel blocker (vasospastic and exertional angina)

Thank you all