Antiarrhythmic drugs

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1. Basic cardiac electrophysiology
   action potential – ion channels – impulse conduction - effective refractory period

2. Mechanism of arrhythmia

3. Proarrhythmic mechanism of antiarrhythmic drugs

4. Frequency dependent effect of antiarrhythmic drugs

5. Classification of antiarrhythmic drugs

6. Individual properties of the antiarrhythmic drugs used in the therapy

7. Brief summary of the therapeutic application of the antiarrhythmic drugs
Na-channel / Na-current from extracellular space to intracellular space

Ca-channel / Ca-current

DEPOLARIZATION

K-channel / K-current from intracellular space to extracellular space

REPOLARIZATION
REFRACTORINESS

**ERP = Effective Refractory Period**
The shortest time needed for reactivation of the heart muscle

Depends on?

1. Repolarization of the myocytes (K-channels)
2. The actual size of the depolarizing currents (Na- and Ca-channels)
1. The speed of depolarization ($V_{\text{max}}$) - depends on fast sodium current

2. Action potential amplitude - depends on fast sodium current

3. Threshold of activation - depends on fast sodium current

4. The cells internal resistance / the resistance between the cells ($r_i$) - depends on the gap junctions

Velocity at which each domino falls

Height of the domino

The energy needed to push the domino

What is the medium resistance (water, air, vacuum)

Sodium channels (atria, ventricle) or calcium channels (sinus and AV-node)
Disorder of the automaticity

Abnormal automaticity I.
EAD = Early AfterDepolarization

OK: Extrem repolarization lengthening
a, hypokalaemia
b, extrem bradycardia
c, genetic malfunction
d, K-channel blockers
(ex. terfenadine, erythromycin, sotalol)

Treatment
a, serum potassium \((K^+)\) elevation
b, magnesium \((Mg^{2+})\)
c, drugs that facilitate repolarization
(ex. mexiletin, verapamil)
Disorder of the automaticity

Abnormal automaticity II.

DAD = Delayed AfterDepolarization

Treatment

decrease of the intracellular calcium level

a) β-receptor blockers (propanolol)
b) Ca-channel antagonists (verapamil)
c) Na-channel blockers (phenytoine, lidocaine)
The re-entry arrhythmias

Antiarrhythmic mechanisms

Proarrhythmic mechanisms
MODULATED RECEPTOR HYPOTHESIS

The binding of a drug depends on the function state of Na\(^+\) or Ca\(^{2+}\) channels.
THE Na$^+$ and Ca$^{2+}$ CHANNEL BLOCKES INHIBIT THE CHANNELS IN A FREQUENCY DEPENDENT MANNER ("USE DEPENDENCY")

The fastest is the heart rate the strongest is the channel inhibition
**Sodium channel inhibition (%)**

- **Fast unbinding (I/B)**
  - lidokaine: 0.13
  - mexiletine: 0.18
  - phenytoine: 0.14
  - amiodarone: 0.28

- **Slow unbinding (I/A és I/C)**
  - quinidine: 5.6
  - prokainamide: 4.5
  - dysopyramide: 37.4
  - flekainide: 15.5
  - enkaidine: 20.3
  - propafenone: 5.4
  - prajmaline: 75.7

**Drug** | $\tau$ (s)
--- | ---
fast unbinding (I/B) |  
- lidokaine | 0.13  
- mexiletine | 0.18  
- phenytoine | 0.14  
- amiodarone | 0.28
slow unbinding (I/A és I/C) |  
- quinidine | 5.6  
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- prajmaline | 75.7
**K⁺-channel blockers**

**REVERSE FREQUENCY DEPENDENCE**

The slower is the frequency, the greater is the lengthening effect of the drug on the repolarization.

Disadvantageous:
1. **Tachycardia** little - ERP lengthening effect
2. **Bradycardia** - extreme lengthening → proarrhythmic, EAD
sinus rhythm (SR) sinus rhythm

vulnerable period extrasystole extrasystole

ERP ERP ERP ERP

1 2 3 4 5 6 7

extrasystole (ES)
The demonstration of the arrhythmogenic effect of the early afterdepolarization (EAD) in canine heart preparations

Control

30 µM SOTALOL

C

Ventricular muscle

Purkinje fibre

ME 2

ME 1

stimulation

50 mV

*
QUINIDINE - Wenkebach, 1914 Frey, 1918
DIRECT cardiac cellular electrophysiological effect:
\( I_{Na}, I_{K} \) and \( I_{Ca} \), inhibition

ECG effect: PQ, QRS and QT lengthening

INDIRECT cardiac effect: anti-cholinergic → facilitation of A-V impulse conduction → paradox tachycardia

SIDE EFFECTS: - hypotension → due to alfa receptor block
- myasthenia gravis → anticholinerg
- negative inotropic → \( I_{Na} \) and/or \( I_{Ca} \) inhibition
- PROARRHYTHMIA → \( I_{K} \) (torsade pointes) and \( I_{Na} \) inhibition impulse conduction related
- tinnitus
- diarrhea
- trombocytopenia
- allergic reatition
INDICATION: atrial fibrillation or supraventricular tachycardias p.o.

CONTRAINDICATION: - heart failure hypotension
    - sick sinus synd. - SA – blokk
    - long QT syndrome, wide QRS
    - glaucoma

DRUG INTERACTION: QUINIDINE + DIGITALIS
**PROCAINAMIDE** - Mautz, 1936

Procaine → local anaestheticum ester-amid less CNS effect

**MECHANISM:** Like quinidine – no anti-cholinergic effect

**INDICATION:** Less popular
- ventricular arrhythmias
- iv / oral application
- activ metabolite N-acetylprocainamide (NAPA) pure class III effect

**SIDE EFFECT:** Proarrhythmia
- special: Lupus erythemasus syndrome (allergic skin reaction, arthralgia, arthrosis)
DISOPYRAMIDE

Mechanism like Quinidine but:
MORE anticholinergic and negative inotropic effect

SIDE EFFECT: - proarrhythmia
  - urine retention
  - negative inotropy

INDICATION: atrial fibrillation, supraventricular arrhythmia
  p.o. i.v.

CONTRAINDICATIONS: myasthenia gravis
  glaucoma
  heart failure
  hypotension
PRAJMALINE

Mechanism like Quinidine but: not-anticholinergic

INDICATION: Brugada syndrome → diagnosis supraventricular arrhythmias

SIDE EFFECTS: proarrhythmia
    haedache
    cholestasis
    visual disturbances
    opstipation
MECHANISM: inhibition of $I_{\text{Na}}$ with fast unbinding kinetics
binding prefers inactivated Na$^+$ channels $\rightarrow$ depolarized ischaemic tissue
postrepolarization refractoriness ERP / APD $\uparrow$
no known effect on other ion channels

INDICATION: only i.v. in ventricular arrhythmias (coronary care unit)
less popular, short half life $t_{1/2} = 1.5 - 2$ h

SIDE EFFECT: CNS $\rightarrow$ tremor, cramps, coma
**MEXILETINE**

**MECHANISM:** like lidocaine but orally active

”oral lidocaine”

**SIDE EFFECT:** toxic and therapeutic serum conc is close

CNS tremor, cramps, coma
bradycardia, negative inotropic
dizziness, confusion

**INDICATION:** ventricular arrhythmia
diabetic neuropathy ?

**CONTRAINDICATION:** impaired A-V conduction

pregnancy, lactation

**PHENYTOINE** → in digitalis arrhythmia

**TOCAINIDE** → bone marrow toxicity
**FLECAINIDE**

**ENCAINIDE**

**MECHANISM:** Strong Na\(^+\) channel inhibition with slow unbinding kinetics from the Na\(^+\) channel.
- Widen QRS at normal heart rate

**SIDE EFFECT:** Proarrhythmia (conduction type) → reentry
- Negative inotropy

**INDICATION:** Atrial fibrillation, supraventricular arrhythmias

**CAST** *(Cardiac Arrhythmia Suppression Trial)*

**PROPAFENONE** Like flecainide but also weak beta receptor inhibition

**CASH** *(Cardiac Arrhythmia Study Hamburg)*
CLASS II effect
BETA ADRENOCEPTOR INHIBITION

**lipophylic drugs**  - metoprolol (selective beta 1 inh)
  - propanolol (Na\(^+\) channel inh)
  - oxprenolol (ISA)
  - pindolol (ISA + Na\(^+\) channel inh)
  - esmolol (acute i.v. t \(\frac{1}{2}\) = 9h)

**Nonlipophylic drugs:**  - atenolol
  - sotalol (racem) (K\(^+\)- channel inhibition repolarization lengthening)

**INDICATION:** supraventricular and ventricular tachycardias (adrenerg backround)
atrial fibrillation, flatter
digitalis intoxication

**CONTRAINDICATION:** - bradycardia
  - AV block
  - asthma bronchiale
**CLASS III effect**

**AMIODARONE** → Chronic oral

**MECHANISM:** repolarization lengthening, $K^+$ channel inhibition / downregulation
QT lengthening
$Na^+$ channel inhibition with fast unbinding kinetics
(lidocaine-like effect)
$Ca^{2+}$ channel inhibition
Beta receptor inhibition

Acute effect → $Na^+$ channel – beta rec – $Ca^{2+}$ channel inhibition

**SIDE EFFECT:** Serious and frequent! Extracardiac
thyroid dysfunction
photodermatitis
hepatocellular necrosis
PULMONARY FIBROSIS ~ 5% X-ray control
cornea deposits
"gray man" syndrome
CNS – GI disturbances
low proarrhythmic risk
**AMIODARONE** → Chronic oral

**INDICATION:** ventricular arrhythmias – heart failure arrhythmias
atrial fibrillation

**APPLICATION:** loading dose 400-600 mg
maintainig dose 200 mg

**PHARMACOKINETIC:** long half life 60-80 days!
**SOTALOL (racem)**

MECHANISM: K⁺ channel inhibition, repolarization lengthening
beta receptor inhibition
dSOTALOL **SWORD (Survival With Oral D-sotalol)**
INDICATION: atrial fibrillation
ventricular tachycardias
$\tau_{1/2} = 15$ óra

**BRETYLIUM**

MECHANISM: K⁺ channel inhibition, repolarization lengthening
adrenerg neuron inhibition
chemical defibrillation
INDICATION: only iv use

**DOFETILIDE**: pure K⁺ channel block (DIAMOND study)

**IBUTILIDE**: indication: atrial fibrillation
CLASS IV effect

**VERAPAMIL**

**MECHANISM:** Ca$^{2+}$ channel inhibition
A-V conduction slowing or block
hypotension, negative inotrop, antianginal

**INDICATION:** paroxismal supraventricular tachycardia
flutter and atrial fibrillation → save ventricle

**CONTRAINDICATION:** heart failure
bradycardia
impaired A-V conduction
new AMI

**INTERACTION:** do not combine with quinidine, beta blockers, dysopyramide

**NIFEDIPINE**

**DILTIAZEM**
OTHER MECHANISMS

ADENOSINE

MECHANISM: indirect Ca\(^{2+}\) channel inhibition $\rightarrow$ purinergic receptor $\rightarrow$ Gi system cAMP↓ = Class IV effect

open adenosine dependent K\(^{+}\) channel $\rightarrow$ hyperpolarization $\rightarrow$ A-V conduction slowing, SA inhibition

IMPORTANT: t \(_{1/2}\) = 10 seconds !!! 6-12 mg iv

INDICATION: supraventricular A-V reentry tachycardias

no side effect
**DIGITALIS**

**MECHANISM:** indirect vagus effect → M receptor → Gi

M receptor dependent K⁺ channels open → hyperpolarization, shortened atrial ERP flatter converted to atrial fibrillation
decrease A-V conduction, increase A-V refractoriness

**INDICATION:** supraventricular tachycardia

**MgSO₄**

**MECHANISM:** Ca²⁺ antagonism

Na⁺ / K⁺ pump inhibition

**INDICATION:** Torsade de pointes tachycardia

**IVABRADINE**

**MECHANISM:** Iᵣ channel inhibition

**INDICATION:** antianginal

heart failure

supraventricular sinus tachyarrhythmia