Antiarrhythmic drugs

Lec1

Pharmacology 4th stage

أ.م.د.اسامة ايوب

- The heart contains specialized cells that exhibit automaticity; they can generate rhythmic action potentials in the absence of external stimuli(pacemaker cells)

- Dysfunction of impulse generation or conduction at any of a number of sites in the heart can cause an abnormality in cardiac rhythm.

- Cardiac arrhythmias may cause the heart
  - ✓ beat too slowly (bradycardia)
  - ✓ beat too rapidly (tachycardia),
  - ✓ irregularly (atrial fibrillation).

- Impulses originating from sites other than the SA node, or impulses traveling along accessory (extra) pathways that lead to deviant depolarizations
  - ✓ AV reentry
  - ✓ Wolff-Parkinson-White syndrome

Causes of arrhythmias

1-Abnormal automaticity

- The SA node shows the fastest rate of Phase 4 depolarization it exhibits a higher rate of discharge than other pacemaker cells exhibiting automaticity.

Causes of arrhythmias

1-Abnormal automaticity

- if cardiac sites other than the SA node show enhanced automaticity, they may generate competing stimuli, and arrhythmias may arise.

- Most of the antiarrhythmic agents suppress automaticity by blocking either Na^+ or Ca^{2+} channels to reduce the ratio of these ions to K^+.

2-Abnormalities in impulse conduction

- Impulses from higher pacemaker centers are normally conducted down pathways that bifurcate to activate the entire ventricular surface.

- This short-circuit pathway results in reexcitation of cardiac muscle, causing premature contraction or a sustained arrhythmia.

Drugs may slow automatic rhythms by altering any of the four determinants of spontaneous pacemaker discharge

1. increase maximum diastolic potential
2. decrease phase 4 slope
3. increase threshold potential
4. prolong action potential duration

CLASSIFICATION OF DRUG	MECHANISM OF ACTION	COMMENT
IA	Na^+ channel blocker	Slows Phase 0 depolarization in ventricular muscle fibers
IB	Na^+ channel blocker	Shortens Phase 3 repolarization in ventricular muscle fibers
IC	Na^+ channel blocker	Markedly slows Phase 0 depolarization in ventricular muscle fibers
II	β-Adrenoreceptor blocker	Inhibits Phase 4 depolarization in SA and AV nodes
III	K^+ channel blocker	Prolongs Phase 3 repolarization in ventricular muscle fibers
IV	Ca^{2+} channel blocker	Inhibits action potential in SA and AV nodes

Figure 17.4
Actions of antiarrhythmic drugs. SA = sinoatrial; AV = atrioventricular.

Class I Antiarrhythmic Drugs

- act by blocking voltage-sensitive sodium channels via the same mechanism as local anesthetics. The decreased rate of entry of sodium slows the rate of rise of Phase 0 of the action potential.

- cause a decrease in excitability and conduction velocity.

- The use has been declining continuously due to their possible proarrhythmic effects, particularly in patients with reduced left ventricular function and ischemic heart disease.

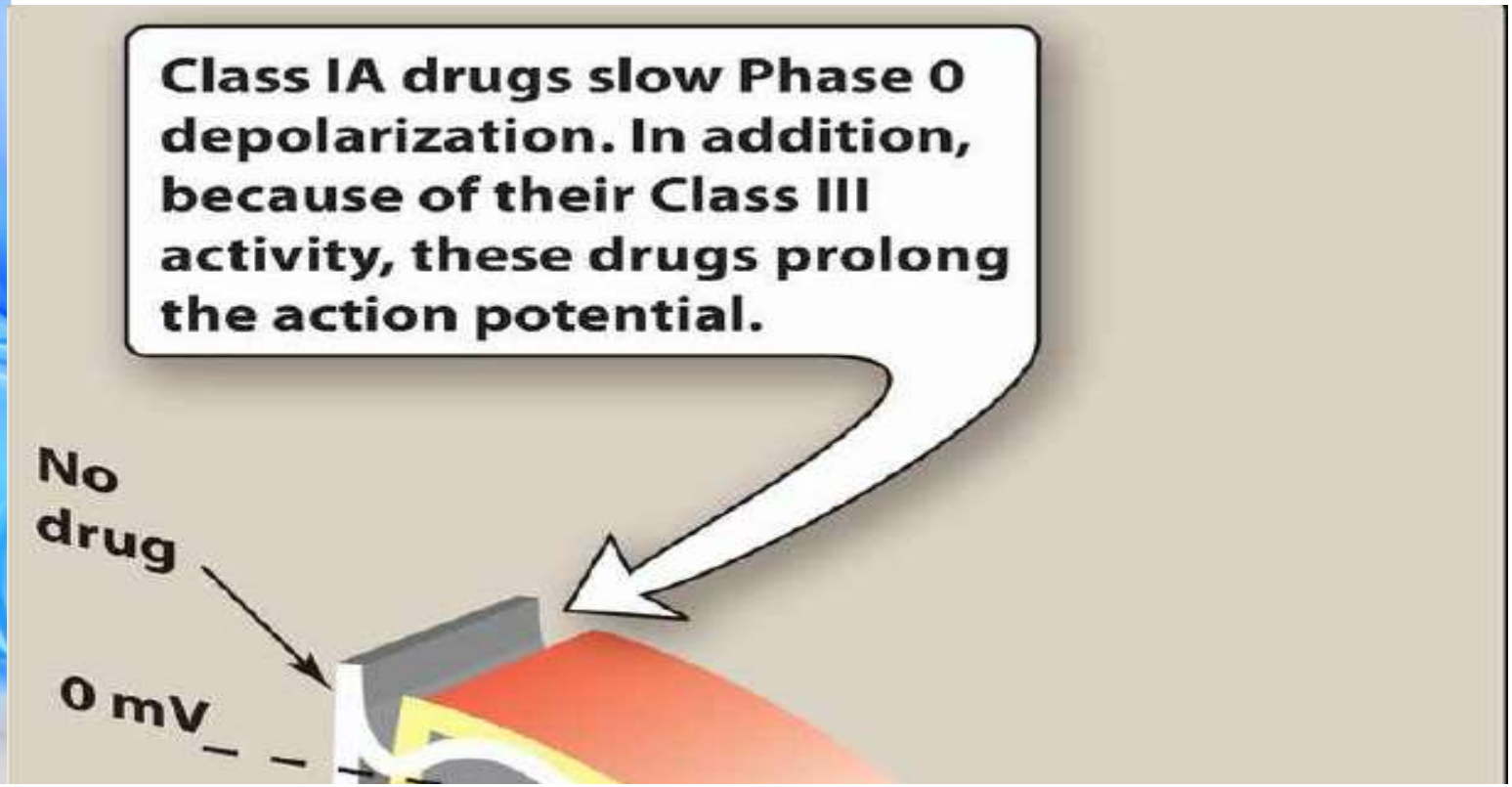
Use-dependence

- Sodium channels exist in three distinct functional states: resting, open and refractory.
- Channels switch rapidly from resting to open in response to depolarisation(activation). Maintained depolarisation, as in ischaemic muscle, causes channels to change more slowly from open to refractory (inactivation),
- it enables these drugs to block cells that are discharging at an abnormally high frequency without interfering with the normal, low-frequency beating of the heart.
- The Class I drugs have been subdivided into three groups according to their effect on the duration of the action potential.

Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

- binds to open and inactivated Na+ channels and prevents Na+ influx, thus slowing the rapid upstroke during phase 0

- It decreases the slope of phase 4 spontaneous depolarization, inhibits K+ channels, and blocks Ca2+ channels



Class IA antiarrhythmic drugs: Quinidine, procainamide, and disopyramide

- **Quinidine also has mild α-adrenergic blocking and anticholinergic actions.**

- **Disopyramide produces a greater negative inotropic effect, and unlike the other drugs, it causes peripheral vasoconstriction**

Therapeutic uses

- Quinidine is used in the treatment of a wide variety of arrhythmias, including atrial, AV junctional, and ventricular tachyarrhythmias.

- Disopyramide can be used as an alternative treatment of ventricular arrhythmias and may also be used for rhythm control in atrial fibrillation or flutter.

Adverse effects

- Due to enhanced proarrhythmic effects and ability to worsen heart failure symptoms, should not be used in patients with atherosclerotic heart disease or systolic heart failure.
-
- Disopyramide has the most anticholinergic adverse effects of the class IA drugs (dry mouth, urinary retention, blurred vision, and constipation).

- Class IB antiarrhythmic drugs: Lidocaine and mexiletine
- The class IB agents rapidly associate and dissociate from Na+ channels.
- The actions are greater when the cardiac cell is depolarized or firing rapidly.
- In addition they shorten phase 3 repolarization and decrease the duration of the action potential
- Neither drug contributes to negative inotropy.

Therapeutic uses

- Although amiodarone is the drug of choice for ventricular fibrillation or ventricular tachycardia, lidocaine may be used as an alternative.

- Mexiletine is used for chronic treatment of ventricular arrhythmias, often in combination with amiodarone.

Pharmacokinetics

- Lidocaine is given intravenously because of extensive first-pass transformation by the liver.
- Lidocaine should be monitored closely when given in combination with drugs affecting these CYP isoenzymes.
- Mexiletine is well absorbed after oral administration. It is metabolized in the liver primarily by CYP2D6 to inactive metabolites and excreted mainly via the biliary route.

Adverse effects

- Lidocaine has a fairly wide therapeutic index. It is primarily metabolised by CYP1A2

- CNS effects include nystagmus (early indicator of toxicity), drowsiness, slurred speech, paresthesia, agitation, confusion, and convulsions, which often limit the duration of continuous infusions.

-

Class IC antiarrhythmic drugs: Flecainide and propafenone

- These drugs slowly dissociate from resting Na+ channels and show prominent effects even at normal heart rates.

- Due to their negative inotropic and proarrhythmic effects, use of these agents is avoided in patients with structural heart disease (left ventricular hypertrophy, heart failure, atherosclerotic heart disease).

Mechanism of action

- Flecainide suppresses phase 0 upstroke in Purkinje and myocardial fibers
- This causes marked slowing of conduction in all cardiac tissue, with a minor effect on the duration of the action potential and refractoriness.
- It possesses weak β-blocking properties.

Therapeutic uses

- Flecainide is useful in the maintenance of sinus rhythm in atrial flutter or fibrillation in patients without structural heart disease and in treating refractory ventricular arrhythmias.

- Use of propafenone is restricted mostly to atrial arrhythmias:

✓ rhythm control of atrial fibrillation or flutter

✓ paroxysmal supraventricular tachycardia prophylaxis in patients with AV reentrant tachycardias.

Adverse effects

- Flecainide is generally well tolerated, with blurred vision, dizziness, and nausea occurring most frequently.

- Propafenone has a similar side effect profile, but may cause bronchospasm and should be avoided in patients with asthma.