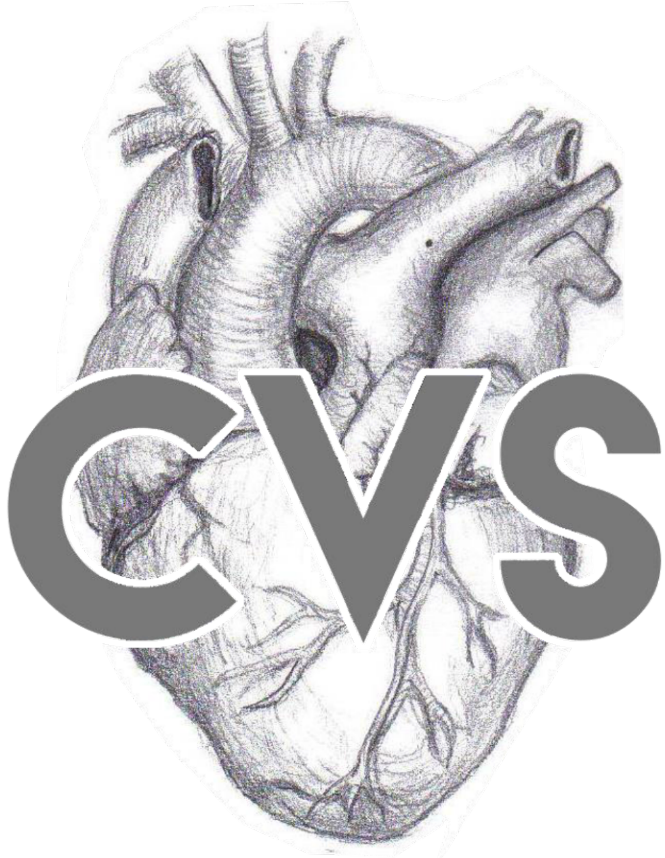

CVS

PHARMACOLOGY

✓Sheet ○Slide ○Handout

Number

10

Subject

Antiarrhythmic drugs

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Date: **00/00/2016**

Price:

Antiarrhythmic drugs

Arrhythmias are dysfunctions cause abnormalities in impulse formation and conduction in the myocardium.

Antiarrhythmic drugs can modify impulse generation and conduction to prevent arrhythmias from occurring or to reduce symptoms associated with arrhythmias.

Antiarrhythmic drugs can be classified according to their predominant effects on the action potential

Class1: Na^+ channel blockers.

Depending on the interaction with the sodium channel, they are subdivided into three subclasses:

Class 1A, 1B and 1C.

Class 1A: intermediate interaction with and dissociation from the channel. This intermediate interaction prolongs the action potential duration and increases the refractory period.

Examples: quinidine, procainamide, disopyramide .

Quinidine- very toxic drug, rarely used.

Class 1B: rapid interaction with and dissociation from the channel → shorten action potential duration.

Examples: lindocaine, phenytoin, tocainide, mexiletine

* Remember:

Lindocaine and phenytoin.

Both are used in digitalis-induced arrhythmias.

Phenytoin – is anti-epileptic drug.

Lindocaine- is anesthetic drug.

Class 1C : slow interaction with and dissociation from the channel → that will not affect the action potential significantly.

Examples: flecainide, propafenone, moricizine .

Class 2: β adrenergic blockers, these drugs:

* decrease heart rate.

*slow conduction through the AV node.

*prolongation of the refractory period of the AV node.

Used in patients with atrial fibrillation and supraventricular tachycardia, because they reduce the impulses going to the ventricle through AV node as a result of the slow conduction through AV node.

Class 3: block potassium channels and thus diminish the outward potassium current during repolarization of cardiac cells _ they affect phase 3.

Examples:

- Amiodarone.

- sotalol_ it is also a β blocker so it is considered mixed class 2 and class 3.

- Bretylium _ very toxic drug.

- ibutilide and dofetilide (they are derived from each other)_ used in patients with supraventricular tachyarrhythmia (atrial fibrillation and supraventricular tachycardia).

Unlike β blockers, dofetilide is effective in **restoring normal sinus** rhythm in patients with atrial fibrillation in certain group of patients.

β blockers don't restore normal sinus rhythm, but they improve the **ventricular rate** in patients with atrial fibrillation.

Atrial fibrillation can lead to ventricular fibrillation because the impulse is conducted through AV node to the ventricles and we do not want that to happen, we want the ventricular rate to be adequate to pump adequate amount of blood to the body. Therefore, we use β blockers as they slow the conduction through AV node and prolong AV refractory period.

Class 4: calcium channel blockers.

* used in supraventricular tachycardia .

Examples: verapamil and diltiazem. but not dihydroperidenes.

**** Dihydroperidenes don't share antiarrhythmic efficacy, they make arrhythmia worse because they increase the heart rate.

Unclassified:

Digoxin, adenosine, magnesium.

Procainamide

Class 1A antiarrhythmic drug .

Cardiac effects:

* Binds to sodium channels and prevents sodium influx thus slowing the rapid upstroke during phase 0 and prolongs the action potential duration, prolongs QRS duration.

* It has direct depressant action on SA & AV nodes (this action is not related to the blockage of Na^+ channels).

Extracardiac effects:

* Ganglion blocking properties

The effect is related to the predominant innervation

In vessels: the predominant innervation is sympathetic therefore, ganglion blocking reduces peripheral vascular resistance and can cause hypotension particularly with IV use or in the presence of left ventricular dysfunction.

In the heart: the predominant innervation is parasympathetic

Blocking the ganglion will result in blocking the parasympathetic increasing the heart rate.

Adverse effects:

- Cardiac:

- Prolongation of QT interval occurs because of the prolongation of the action potential.

- induction of torsade de pointes (https://www.youtube.com/watch?v=BP-bhb0MhB4)

Torsade de pointes also called polymorphic ventricular tachycardia.

- all antiarrhythmic drugs can produce arrhythmia as a side effect

- Extracardiac toxicity:

- Lupus erythematous like syndrome: arthralgia, arthritis, pleuritis, pericarditis and parenchymal pulmonary disease, with rare renal impairment.

-Reversible if you stop the drug.

During long term therapy ANA-antinuclear antibodies occur in 100% of patients. But not all of them develop lupus erythematous-like syndrome (third of them will develop lupus erythematous like syndrome).

> **Systemic lupus erythematous** is an autoimmune disease in which the body's immune system mistakenly attacks the tissue, affects all parts of the body
>
> **lupus erythematous like syndrome**: affects all parts of the body except the kidney

Pharmacokinetics:

-Procainamide is acetylated in the liver to N- acetyl procainamide (NAPA).

-NAPA has class 3 antiarrhythmic activity → affects potassium channels not sodium channels.

-Excessive accumulation of NAPA has been implicated in torsade de pointes during procainamide therapy especially in patients with renal failure .

* There is polymorphic acetylation in the population _ in Jordan third of the population are rapid acetylators, 2/3 of the population are slow acetylators.

-Lupus syndrome is more common in slow acytlators because there is more accumulation of the drug.

Therapeutic uses:

* Effective against most atrial and ventricular arrhythmias, but long-term use should be avoided because of lupus syndrome.

* Second or third choice after lidocaine and amiodarone for treatment of sustained ventricular arrhythmias associated with acute myocardial infarction (this therapeutic use is not required for the sake of the exam).

Disoperamide

- Class 1A.
- The effects are very similar to those of procainamide.
- It has antimuscarinic effect (atropine-like effects).
- Indicated for treatment of ventricular arrhythmias?

The difference between procainamide and disoperamide
Procainamide has ganglion block effect.
Disoperamide has antimuscarinic effect.
Otherwise, they are similar.

Toxicity:

* It has antimiscarinic negative inotropic effect and may precipitate heart failure and thus it is not used as a first line antiarrhythmic agent. It should not be used in patients with heart failure.

Disoperamide is antimuscarinic drug, so how does it reduce contraction?

By the direct depressant action on SA & AV node (like procainamide) → less contraction.

* Atropine-like effects

Know the ABCD's of antimuscarinic side effects:

Anorexia

Bllury vision

Constipation

Dry mouth + **dry** sweating

Stasis of urine (retention of urine)

And **tachycardia**

Lidocaine

- Class 1B : blocks sodium channel with rapid interaction kinetic
- Shortens action potential duration.
  Short action potential → short refractory period
- It has greater effect on purkinje and ventricular cells .

Toxicity:

The two major categories of the adverse effects of lidocaine are neurologic and cardiac

Cardiac:

- proarrythmic effect (as we said before all antiarrhythmic drugs can cause arrhythmias in toxic doses).

SA arrest, worsening of impaired conduction and ventricular arrhythmias.

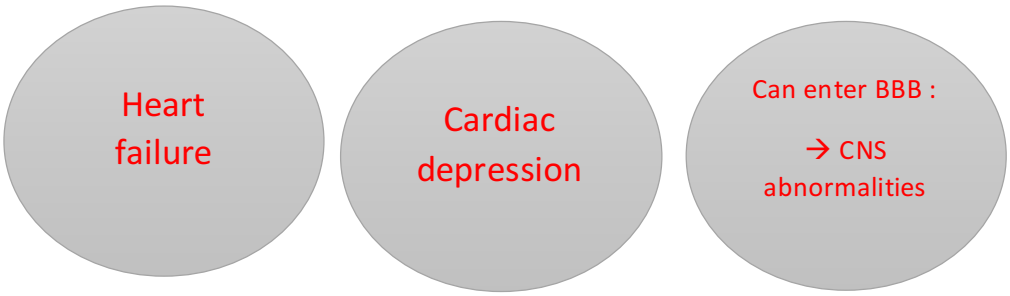
Extracardiac:

Neurologic:

Paraesthesias, tremor, nausea, lightheadedness, hearing disturbances, slurred speech and **convulsions** especially in elderly or with rapid bolus IV injection.

After rapid bolus AV injection lidocaine causes cardiac depression, it is very dangerous.

Lidocaine is delivered by infusion, that is why it is used for a short period then it is replaced by another drug (short-term treatment administration).



Paresthesia

Tremors

…….

(The neurological effects above)

And **convulsions**

Tocainide – like lidocaine, oral form.

For termination of arrhythmia lidocaine **not given by IV bolus injection**, *lidocaine should be administrated in the form of IV infusion*

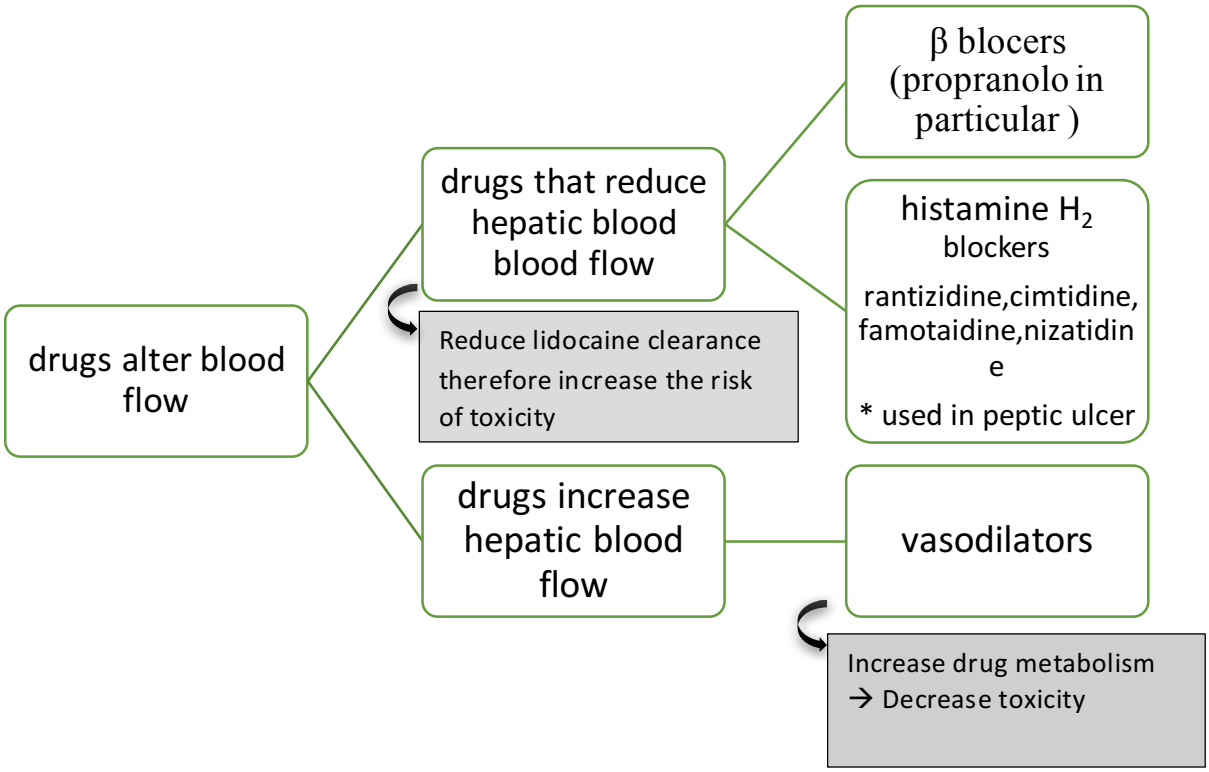
IV bolus injection of lidocaine causes:

The drugs we talked about are toxic drugs with low therapeutic index.

Lidocaine undergoes extensive first pass metabolism (high extraction ration drugs)

Which means that the metabolism is affected by blood flow.

- ☒ Drugs that reduce blood flow will reduce metabolism of lidocaine and increase its toxicity.
- ☒ Drugs that increase blood flow will increase the metabolism and reduce the <u>effect</u> and <u>toxicity</u> of lidocaine



- **<u>Protein binding of the drug:</u>**

The bound portion of the drug is not available for action and not available for elimination.

The free portion is the portion that will have an effect and will be eliminated.

Lidocaine is bound to α_1 acid glycoprotein (protein present in the circulation it binds basic drugs, lidocaine is a basic drug).

α_1 acid glycoprotein is acute phase reactant.

When α_1 acid glycoprotein increases, lidocaine binding to it increases → free portion decrease → less action.

Therefore, patients with elevated α_1 acid glycoprotein need higher dose of the drug.

Acute phase reactant: class of proteins whose plasma concentration increase in response to diseases, acute inflammation, cancers, MI…)

Ook! We can solve this problem by increasing the dose.

However, there is another problem, during treatment α_1 acid glycoprotein concentration drops (remember it is acute phase reactant) resulting in lidocaine toxicity (⬆free portion→ produce more effect).

Therapeutic uses:

* Remember lidocaine (and phenytoin) is used in digitalis-induced arrhythmias.

* lidocaine is the first drug of choice for ischemia-induced arrhythmia.

Prophylactic use (lidocaine IV infusion) in the setting of MI to prevent arrhythmia (Not to treat) was associated with increased *mortality*, so lidocaine is not used for prophylaxis.

* used for treatment of arrhythmia and ischemia.

Flecainide

- Class 1C.
- Is a potent blocker of Na^+ and k^+ channels with slow unblocking kinetics.
  * note that although it does block certain k^+ channels, it doesn't prolong the action potential or the QT interval.
- Very effective in suppressing premature ventricular contractions (ectopic beats). However, it may induce arrhythmia and increase the mortality, so flecainide shouldn't be used in this case , β blockers are better and safer in this condition.
- **Flecainide used only for supraventricular arrhythmias (atrial fibrillation and supraventricular tachycardia) in patients with <u>normal heart.</u>**

Propafenone

- Mixed class 1 and class 2.
- It's sodium channel blocker.
- Has ***weak*** β-blocking activity.
- Most common adverse effects are metallic taste, constipation and arrhythmia exacerbation.
- Used primarily for supraventricular arrhythmia.

β- Blockers

- Reduce HR , reduce AV conduction , prolong effective refractory period in AV node → prevent atrial impulses from reaching the ventricles.
- Used in atrial fibrillation and flutter to control ventricular rate.
- Used in wolf- Parkinson – white syndrome in combination with sodium channel blockers.

Amiodarone

-Mainly class 3.

-Wide spectrum antiarrhythmic agent, which means that you can use it for atrial arrhythmias and for ventricular arrhythmias.

- Usually atrial arrhythmias require lower dose.

Cardiac effects:

- It's dominant effect is prolongation of action potential and refractory period by blocking k^+ channels .
  Doesn't cause polymorphic ventricular tachycardia (although the action potential duration is prolonged).
- blocks sodium channels.
  It has weak adrenergic and ca^{+2} channel blocking actions.

Extracardiac effects:

- Peripheral vasodilation.
  Amiodarone first was used in treatment of angina because of its β blocker action and vasodilator action but they figured out that it is not effective in angina. Now it is used as antiarrhythmic drug.

Toxicity:

Cardiac:

- Bradycardia and heart block in patients with preexisting sinus or AV node disease (previous disease).

Extracardiac:

Extracadiac toxicity of amiodarone is much more significant.

* **Dose related pulmonary toxicity _** the most significant adverse effect

Fatal pulmonary fibrosis → there's no oxygen exchange→ hypoxia.

* Abnormal liver function tests: because of abnormal allergic reaction in the liver- hypersensitivity hepatitis.

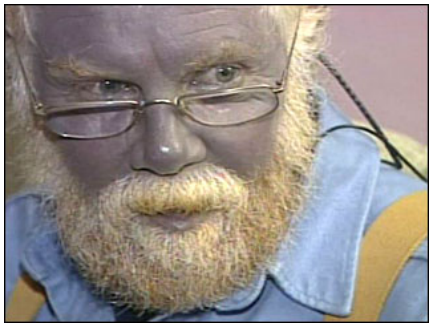
Before using amiodarone, you need to monitor liver functions, while using amiodarone you have to check hepatic function again.

* Skin deposit and photodermatitis :

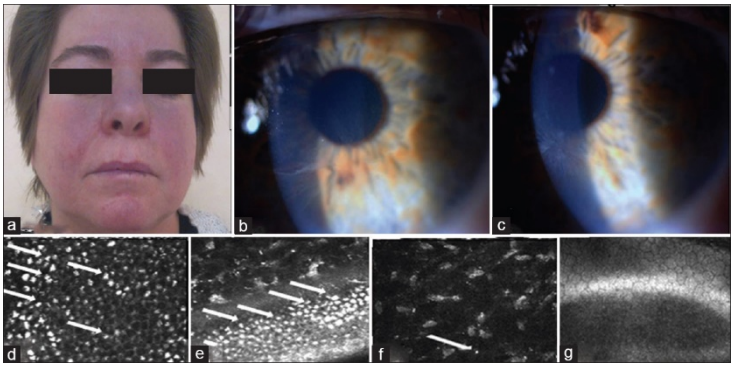
Photodermatitis – dermatitis triggered by exposure to sun light or UV light

Deposits due to the drug

Amiodarone itself precipitate which increase or UV light with – it is a cosmetic

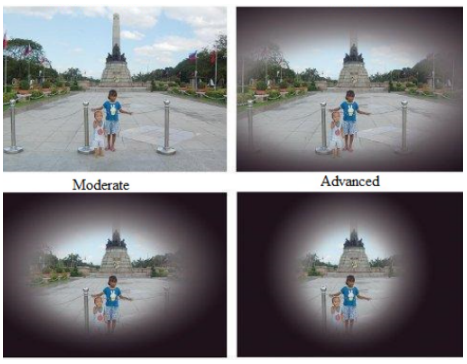


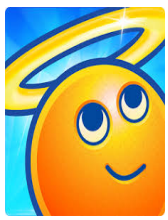
in the skin→ inflammation in the presence of sun light gray blue skin discoloration problem.



* Asymptomatic corneal microdensities in almost all patients.

* halos deveolop in the peripheral visual fields of some patients, that doesn't require stopping the drug.

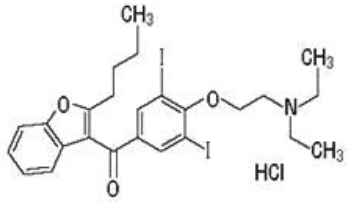




* Rarely, optic neuriritis may progress to blindness.

* It blocks peripheral conversion of T_4 into T_3 it is also a potential source of large amounts of organic iodine. Thus, it may result in hypo- or hyperthyroidism. Thyroid function should be evaluated before initiating treatment and should be moinitored periodically

amiodarone chemical structure →



Hyperthyroidism is a risk factor for atrial fibrillation. Thyroxin should be measured initially in the patients with atrial fibrillation (T_4, T_3).

Hyperthyroidism causes upregulation of β receptors and excessive stimulation to the heart; this can result in supraventricular arrhythmia or atrial fibrillation.

Pharmacokinetics:

* Low bioavailability (~50%).

* It undergoes hepatic metabolism (CYP3A4) and the major metabolite desethylamiodarone is bioactive .

-Drug- drug interaction.

*it accumulates in many tissues including the heart (10-50X plasma), lung, liver, skin, and is concentrated in tears.

*long half life.

-Initial half-life 3-10 days, terminal half-life several weeks (1-3 weeks).

Following discontinuation of the drug, effects are maintained for 1-3 months, and measurable tissue levels may be observed after 1 year.

-We reach steady state after four half lives of administration.

So → 4*50 = 200 days (7 months)

I can't wait 7 months to reach the therapeutic concentration (to treat patient with arrhythmia), the patient will die.

In order to reach the therapeutic concentration in a short period of time we give the patient loading dose, the loading dose is given gradually because of the high tissue binding.

- Drug interactions;

-Tremendous. All other medications should be reviewed when the drug is initiated and when the dose is adjusted.

* Its levels are increased by inhibitors of CYP3A4 (cimetidine).

* Its levels are reduced by inducers of CYP3A4 (rifampin).

* It inhibits many cytochrome p450 enzymes and may result in high levels of many drugs including ***statins, digoxin and warfarin***

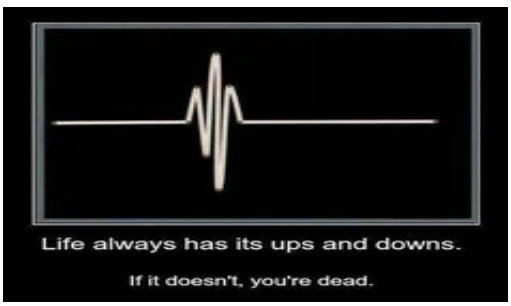
- The dose of warfarin should be reduced by one third to one half following initiation of amiodarone and prothrombin times should be closely monitored

Therapeutic use:

Low dose – atrial fibrillation.

High dose- ventricular arrhythmias.

Low incidence of torsade de pointes.



The end …

You can read the summary for better understanding

Good luck

Reem Ahmad Awawdeh

Antiarrhythmic drugs

Class 1

Na^+ channel blockers

1A: prolong action potential (intermediate interaction)
- Quinidine
- Procainamide
- Disopyramide

1B: short action potential (rapid interaction)
- lindocaine

1C: minimal effect on AP (slow interaction)
- Flecainide
- Propafenone

Class 2

β-blockers
- ↓ HR
- ↓ conduction through AV node
- prolong refractory period of AV node
- Propranolol
- atenolol
- esmolol

Class 5

unclassified
- digoxin
- adenosine
- magnesium

Class 3

K^+ channel blocker

prolong action potential duration
- Amiodarone

Class 4

Ca^{+2} channel blockers

↓ SA rate

prolong conduction time & refractory period.
- Verapamil
- diltiazem

not dihydropyridine

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time & refractory period.
- Verapamil
- diltiazem

not dihydropyridine

Class 1A Na^+ channel blocker

Procainamide

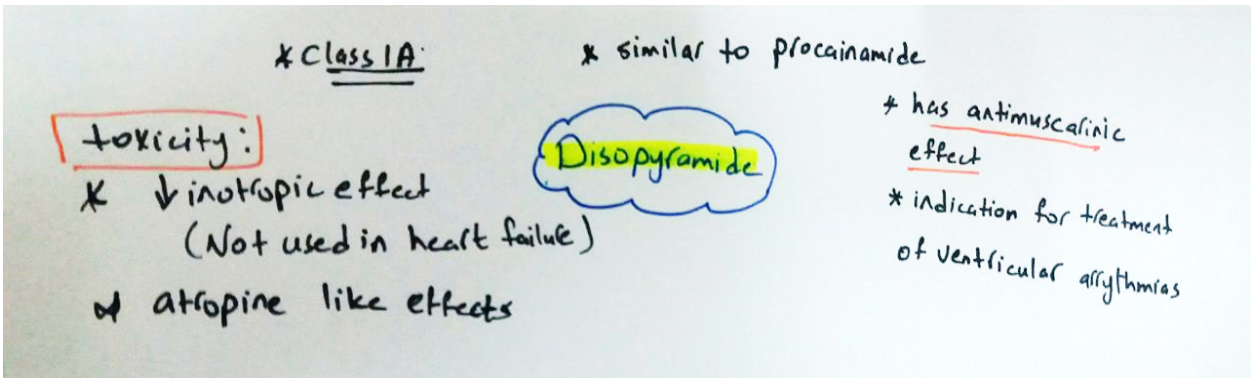
Ganglion blocking properties

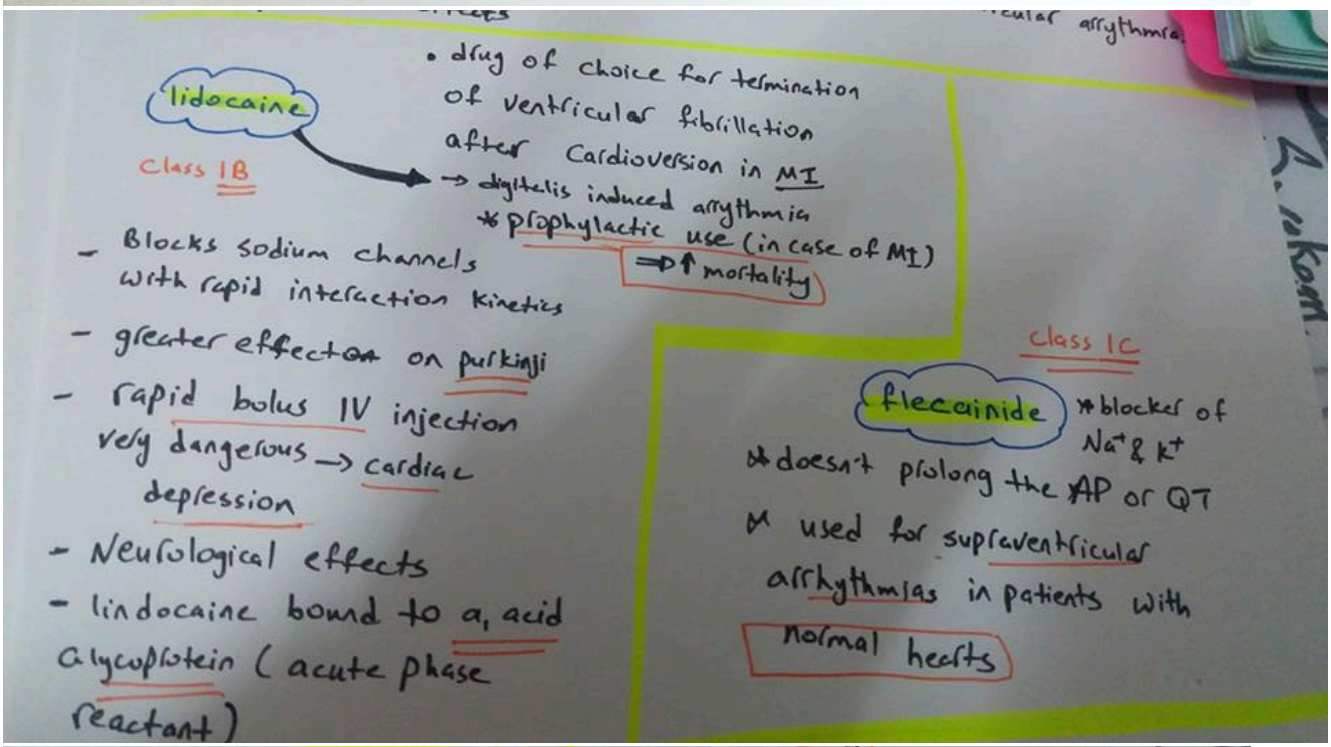
Vessels → vasodilation → hypotention

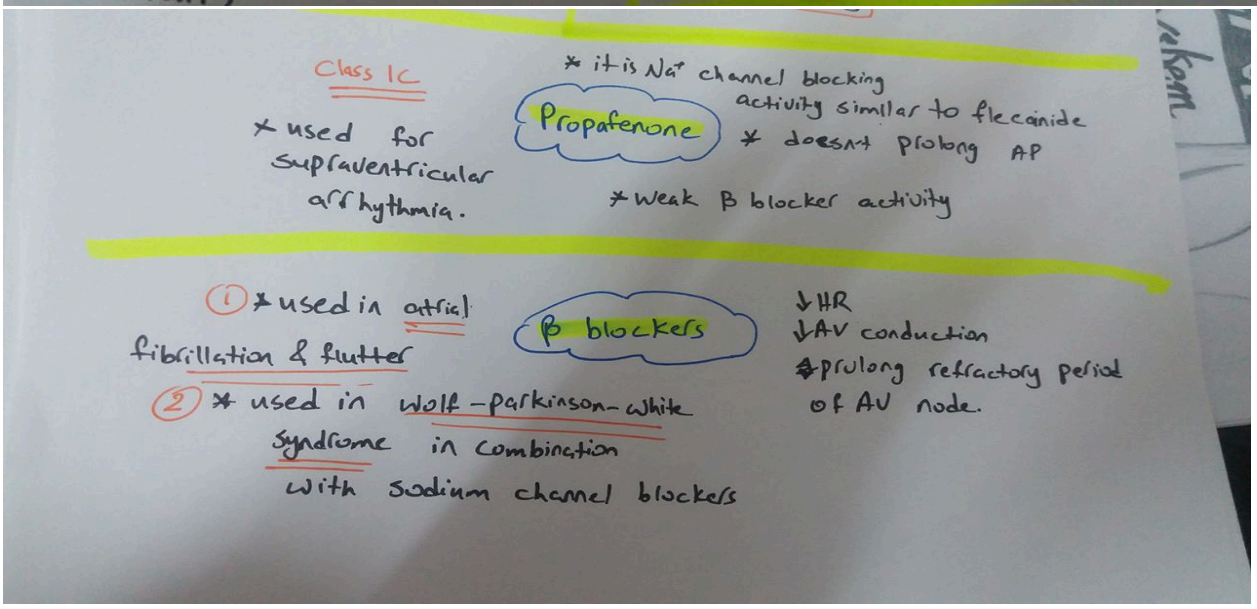
Heart → ↑ Heart rate

*used in atrial & Ventricular arrhythmias but long term use should be avoided.

adverse effects
- * prolongation of AP → torsade de pointes
- * lupus erythmetous like syndrome (reversible)


*Class IA
* similar to procainamide
toxicity:
* ↓inotropic effect
(Not used in heart failure)
atropine like effects
Disopyramide
* has antimuscarinic effect
* indication for treatment of ventricular arrythmias


lidocaine
Class IB
• drug of choice for termination of ventricular fibrillation after Cardioversion in MI
→ digitalis induced arrythmia
* prophylactic use (in case of MI)
⇒ ↑ mortality
- Blocks sodium channels with rapid interaction kinetics
- greater effect on purkinji
- rapid bolus IV injection very dangerous → cardiac depression
- Neurological effects
- lindocaine bound to a1 acid glycoprotein (acute phase reactant)
Class IC
flecainide
* blocker of Na+ & K+
* doesn't prolong the AP or QT
* used for supraventricular arrhythmias in patients with normal hearts


Class IC
* used for supraventricular arrhythmia.
Propafenone
* it is Na+ channel blocking activity similar to flecainide
* doesn't prolong AP
* Weak β blocker activity
β blockers
① * used in atrial fibrillation & flutter
② * used in Wolf-parkinson-White Syndrome in combination with sodium channel blockers
↓HR
↓AV conduction
↑prolong refractory period of AV node.

Amiodarone

* mainly class 3
  blockage of K^+ channels.
  - prolong AP
  - has weak adrenergic and Ca^{+2} channel blocking action
    → slowing heart rate & AV conduction
    → peripheral vasodilation

*Antiarrhythmic wide-spectrum

*toxicity

- → bradycardia & heart block in patients with preexisting sinus or AV node disease
- → dose related pulmonary toxicity → pulmonary fibrosis
- → hypersensitivity hepatitis.
- → photodermatitis
- → coroneal microdensities in almost all patients
- → Halos
- → hypo / ~~hyperthyroidism~~ hyperthyroidism.

*metabolized by CYP3A4

*metabolized by CYP3A4 (drug-drug interaction)

*accumulated in many tissues

* long half life (effects maintained for 1-3 months after & measurable levels observed ~~after~~ after 1 year.

* inhibits many cytochrome P450 enzymes ← ↑ levels of many drugs

Statins | digoxin | warfarin

uses:

low dose — atrial fibrillation

high dose — Ventricular tachycardia.

Good luck ♥ ^^