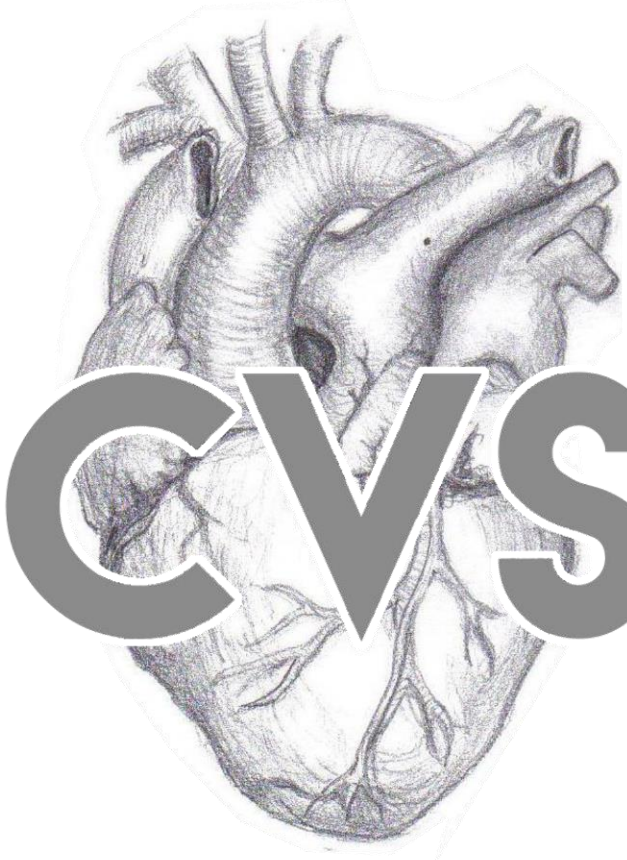

CVS

PHARMACOLOGY

Sheet ○ Slide ○ Handout

Number

8

Subject

Treatment of heart failure#3 + Intro to antiarrhythmics

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Date: **00/00/2016**

Price:

Digitalis-

❖ Therapeutic uses:

1. Heart failure (↑contractility)- in **systolic dysfunction** but not diastolic.
   Most helpful in patients with dilated hearts..
   **Dilation of the heart here is the one related to passive stretch rather than that caused by remodeling of the heart.
   (Remodeling of the heart which causes dilation of the heart is one of the factors responsible for the diastolic dysfunction. but that is not related to the passive stress. What digoxin works for is the dilation related to passive stress (it is a systolic dysfunction but dilation of the heart happens because of fluid overload).
   Usually given after ACEIs.
   Response rate ~ 50% or less (not all pt. will benefit from digoxin

2. If HF is due to Atrial fibrillation this drug will treat both (↓conduction through the AV node) this will **not** allow **all** atrial impulses to reach the ventricle. This means that the sinus rhythm in the SA node will not be recovered (the SA impulse will not reach the ventricles)
   Therapeutic range 0.8-2 ng/ mL(~1). Toxicity appears above 1.5 ng/mL. Atrial-Fibrillation may require higher concentrations. (if you were to give higher concentrations, then you become so near or even exceed the toxic dose, Meaning: →
   very narrow therapeutic index, there's actually an overlap b/w therapeutic and toxic doses.)

Do not improve mortality

Quick reminder:
K^+ competes with digoxin and therefore a decrease in potassium will enhance the binding of digoxin

❖ Interactions:

1. **↓K^+ , ↓Mg^{+2}, ↑Ca^{+2}**
2. **Quinidine:** displaces digoxin from tissue binding sites (digoxin binds to muscles/ skeletal and cardiac) so the volume of distribution to the tissue is decreased(so the free conc. is increased which increase toxicity) …Also, clearance is decreased and therefore enhances toxicity.
   Clearance: volume of blood that is cleared from the drug completely per unit time. If you remember from the introductory course:
   $$CL = \lambda * Vd$$
   Clearance= 1st order elimination rate constant * Volume of distribution
   This equation shows that clearance is proportional to elimination and to Vd (A measure of elimination as well as distribution) The drug follows first order kinetics and therefore If Vd decreases the clearance decreases provided that the half life is the same (elimination rate is constant depends on the t1/2 because t1/2 * elimination rate constant= 0.7)
   And that applies here because when Vd for digoxin decreases as a result of quinidine displacing it from its tissue binding cites its clearance will decrease.

3. **Agents which release catecholamines sensitize the myocardium to digitalis induced arrhythmias** (Both are positive inotropic agents)

❖ Contraindications

Wolff-Parkinson-White Syndrome (SEE THE FIGURE ON PAGE 5)

- Congenital Syndrome Caused by an accessory bundle called: the **bundle of kent.**

*manifested by: paroxysmal tachycardia OR atrial fibrillation

*SA and AV nodes are slow conductive pathways; they utilize Calcium for conduction of the AP.

*This accessory bundle (Kent) present on those patients is not calcium dependent but Na+ dependent and therefore it is a fast conduction pathway. It may conduct the impulse in the reverse direction.

*if you slow the already slow pathway (the AV node) further through giving digitalis you are allowing the fast pathway to act which results in circus movement in the AV node causing a-fib. And further arrhythmia (the impulse will return back to the atrium)

*So you should NEVER use digitalis for the treatment of arrhythmia associated with Wolff-Parkinson-White syndrome UNLESS you give Na channel blockers to inhibit the accessory pathway.

*This syndrome can be treated by using electrophysiological mapping to determine the location of this accessory bundle, then we do ablation(اتلاف) to this bundle.

❖ Management of toxicity:

(You have to do something about it because its toxicity is bad and it stays for nearly a week (long half life))

1. Stop the drug
2. ECG monitoring
3. Measure serum level of the drug (low therapeutic index)\
4. *Correct electrolytes imbalance(Na, K, Ca, Mg)* (remember that hypokalemia, hypomagnesemia and hypercalcemia all increase the toxicity of the drug, so if you do not correct them you won't correct the toxicity) and that applies to all patients with arrhythmia because by doing that you might reverse the arrhythmia all by all.
5. Use antibodies toward digoxin to get rid of digitalis
6. antiarrhythmic – (specific for digitalis induced arrhythmia) **lidocaine** OR **phenytoin** ONLY which are sodium channel blockers and *not any other antiarrhythmics*

***Cardioversion-electrical shock** to the heart to reverse the arrhythmia and recover the sinus rhythm especially used in ventricular arrhythmia.

IMP>>All digitalis induced arrhythmias become worse with cardioversion except ventricular fibrillation. So **DO NOT use cardioversion in digitalis toxicity <u>except</u> in the case of ventricular fibrillation.

*extremely narrow therapeutic index and may not decrease mortality in chronic heart failure.

Other Positive Inotropes- Safer than digitalis or at least their therapeutic index is not narrow.

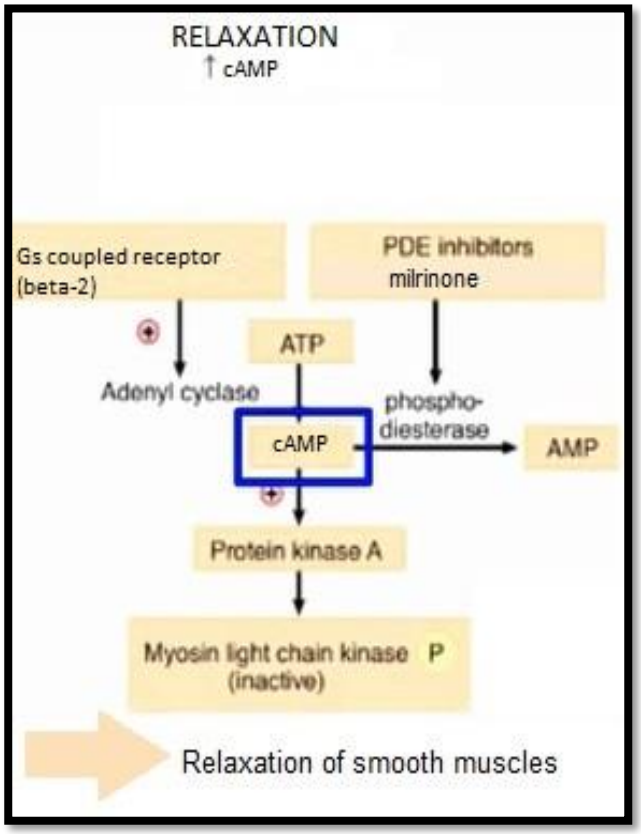
1. **Milrinone (Bipyridines)** rarely used
2. **β 1 -Adrenoceptor <u>agonists:</u> Dobutamine**- more commonly used

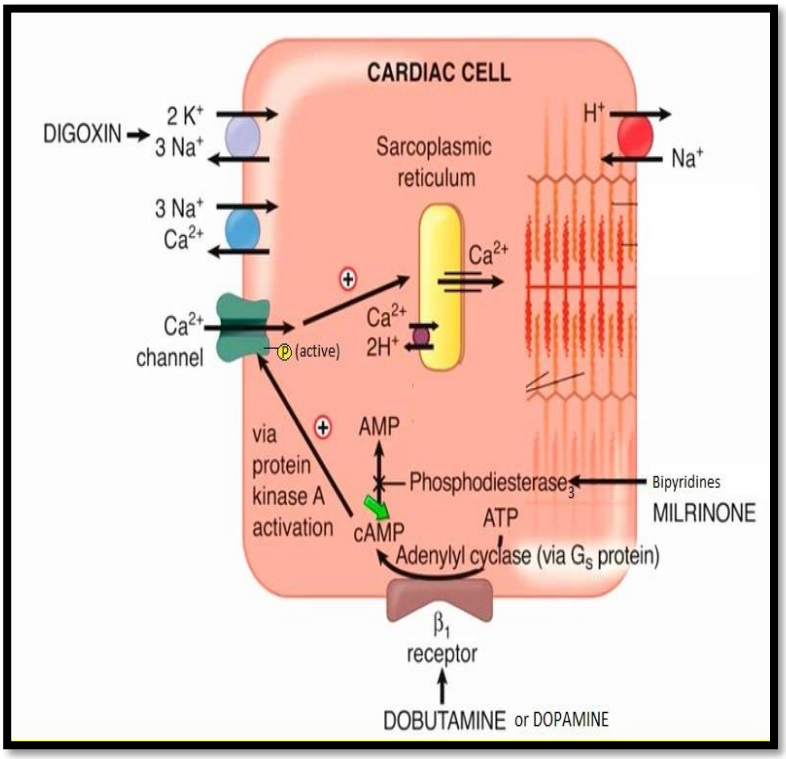
These drugs are given to hospitalized (IV effusion) patients and are not for home use. (Digitalis is a "Home" drug)

❖ Milrinone- Phosphodiesterase isozyme 3 inhibitor

-↑cAMP in heart muscle; results in **↑inotropy**
This effect is due to increase in Ca^{2+} influx, there might be an effect on calcium of the Sarcoplasmic reticulum.
-↑cAMP in smooth muscle; results in **vasodilation** → ↓TPR → ↓afterload

To fully understand this look into these two figures- they are extra..





*Toxicity includes nausea and vomiting; arrhythmias (Similar to digoxin) but it is not a narrow therapeutic index drug.

Usually used intravenously and only fo acute heart failure or severe exacerbation of chromic heart failure.

NOTE: Any drug that stimulate the heart (Digitalis, epinephrine…) can cause arrhythmia.

❖ Dobutamine- Selective β-1 adrenergic agonist

- "Oral Dopamine"! (it was designed to be given orally)

-Act on ONE receptor

-increase both heart rate and contractility in the heart. But effect is actually more inotropic than chronotropic. However, it might increase HR to the extent in which it will cause tachycardia which will decrease the filling time and increase O_2 demand and so it might cause myocardial ischemia in certain patients.

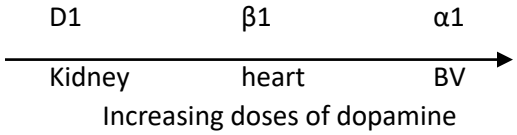
-Tolerance develops (**tachyphylaxis**; that is **RAPID tolerance**) due to internalization of the receptor.

Tolerance: Less response to the drug (diminished action)that develop with continuous administration. It occurs due to down regulation (decrease in number) of the receptors through: A) internalization and endocytosis of the receptors (fastest mechanism) B) on the long term down regulation is on the gene level.

-This problem is solved by giving *intermittent infusions*, for the receptors to recover in the period when no drug is available.

❖ Dopamine

- Never given Orally
- can also be used because it acts on 3 receptors (not at the same time; but effect is dose-dependent)



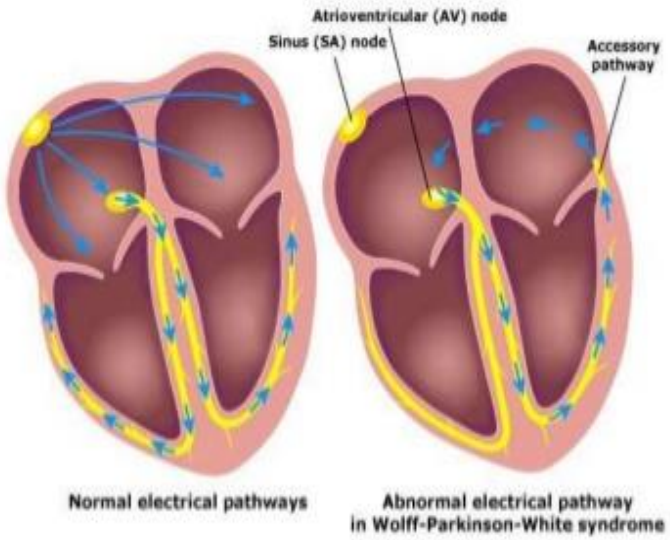
Increasing doses of dopamine

As you can see low doses of dopamine stimulates D receptors only . D receptors are mainly in the kidney so dopamine is excellent for shock ; normally the kidneys get a large blood supply, in shock blood flow to the kidneys decreases, So a low dose (Called Renal dose) of dopamine will dilate

renal arterioles, increase renal blood flow and protect the kidney from ischemia .
If you increase the dose a little bit you will stimulate β receptors on the heart→ positive inotropy & increase in the heart rate.

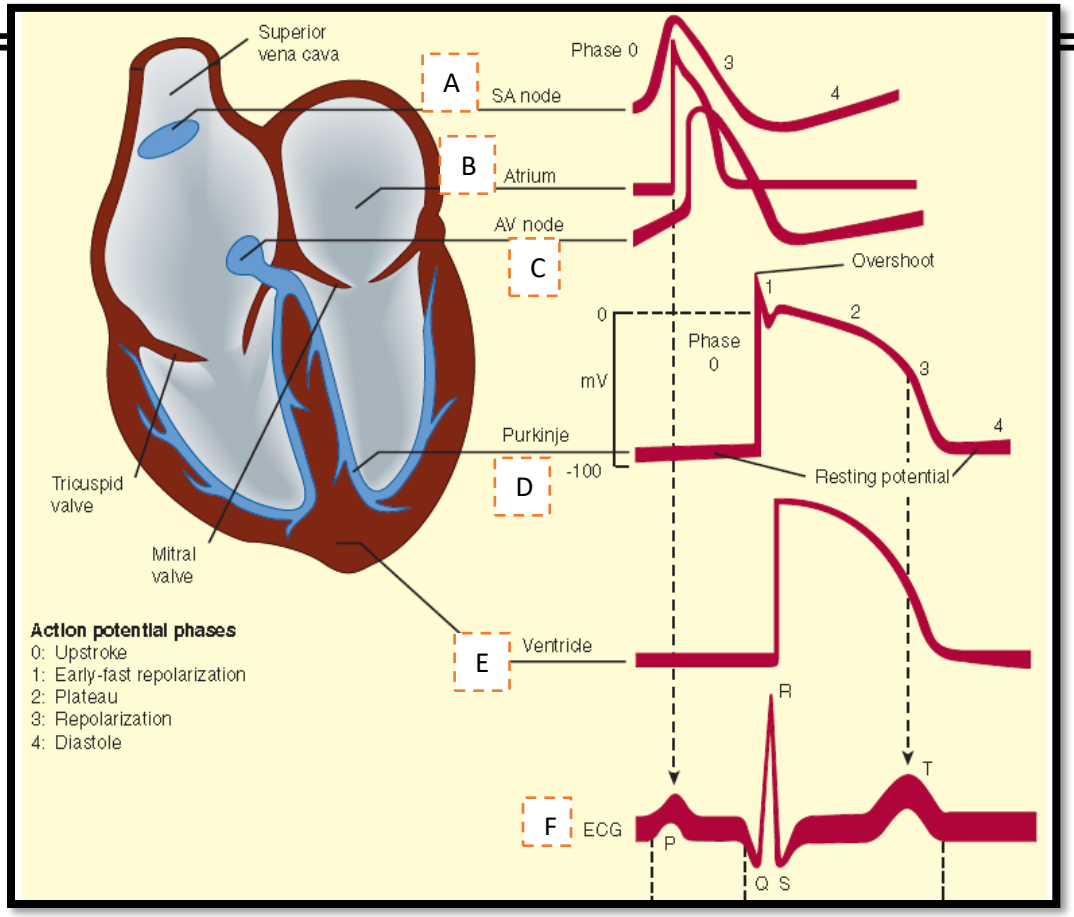
-A large dose will stimulate α receptors and now dopamine is no more effective on D receptors, rather, it will cause systemic vasoconstriction (damage to the kidney!) and so an increase in blood pressure, So If you need to increase blood pressure in a pt. with HF give a large dose of dopamine. (At this dose, we can use Dopamine for the treatment of heart failure if the patient already has Hypotension.)

…with Bundle of Kent



And that ends the talk about Heart Failure..

NEXT PAGE.. Antiarrhythmic (revision of normal physiology)



Antiarrhythmic Drugs

In A, B, C, D and E we are recording intracellularly, But in F (ECG) we are recording from the surface of the body and we are talking about the electrical activity of the heart as a whole.
-If we compared phase 4 of the action potential in the AV and SA node to that in the ventricular muscles we will notice that in A, C and D there is a slope which indicates spontaneous depolarization; meaning: these tissues can generate action potential by themselves, but the driving force for all of them is the SA node. If the SA node was necrotic, etc the AV node will become the pacemaker and if it also was defective, then purkinje fibers takes the job, That is because all of these tissues have automaticity.

The SA node rhythm is the normal rhythm and Without the SA node we actually have an arrhythmia.

If the AV node is not working that will also cause an arrhythmia (the basis for heart block)

- Ventricular muscle are not autorythmic at all, BUT the atrial muscles have a fossae for ectopic pace maker but they're normally suppressed by the action of the SA node.

Now let's compare the upstroke (phase0); in the SA and AV node this upstroke is slow (hence the name; slow conducting tissues)and is caused by $Ca^{2=}$ influx, So slow conducting tissues utilize calcium for depolarization (and a little bit of sodium as well)
His, purkinje system and the ventricle: rapidly conducting tissues, caused by Na^{+} influx.

Repolarization: Potassium efflux

His Purkinje system: phase1 is caused by the **closure of sodium channels** followed by oscillatory $Ca^{2=}$ entry (phase2) —Previously phase1 was thought to be the result of chloride entry. At phase3 potassium causes repolarization

NOTES:

1- There are many types of K+ channels but we are going to consider the as one type.

2- I_f is responsible for the spontaneous depolarization and it is different from other currents because it is a mixed Na and K current, it is activated by hyperpolarization.