Digitalis Toxicity

Lab 7

Assistant lecturer

Nada S. Shaker

- A group of pharmacologically active compounds are extracted mostly from the leaves and in pure form are referred to by common chemical names such as ***digitoxin*** or ***digoxin***,
- The two drugs differ in that Digoxin has an additional hydroxyl group. So it is eliminated from the body via the kidneys, while **Digitoxin** is eliminated via the liver, & and could be used in patients with poor or erratic kidney function.

Measurements	digoxin	digitoxin
Onset time	1.5 – 6 hr	3-6 hr
peak	4-6 hr	6-12 hr
T 0.5	31-40 hr	4-6 days
Protein binding	20-25 %	90-97%
Vd	7-8L/kg	0.6L/Kg
Excretion route	Renal 75%	Hepatic 80%
Toxic blood level	2.4 ng/mL	over 30 ng/mL

Mechanism of action

Digitalis works by

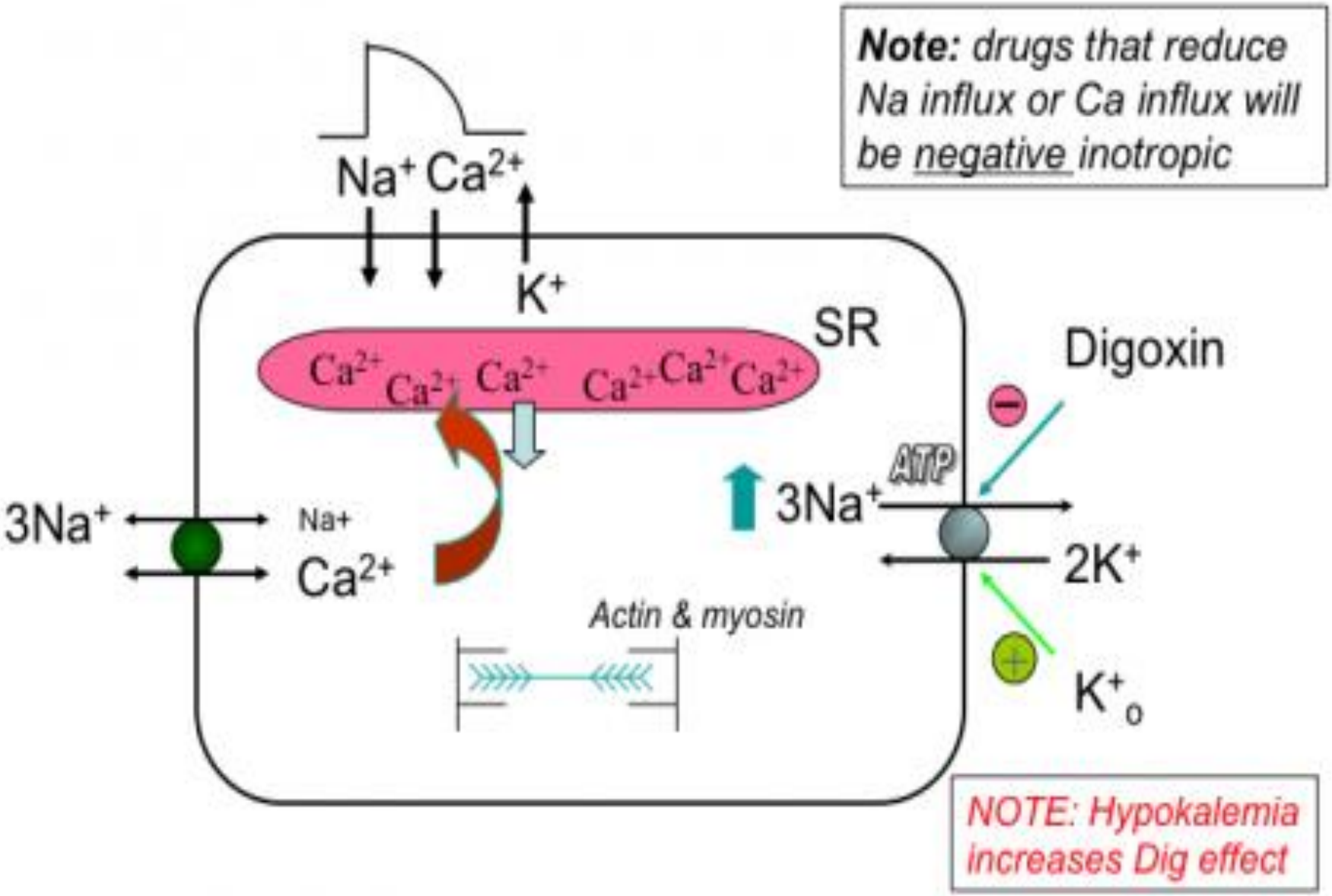
inhibiting sodium-potassium ATPase.

increased intracellular concentration of Na ion decreased concentration gradient across the cell membrane.

This increase in intracellular Na is then used as a driving force for the Na-Ca pump to bring Ca ions into the cell.

- This increased cytosolic calcium ion concentration results in increased calcium ion storage in the sarcoplasmic reticulum.
- Upon action potential (cardiac contraction) more calcium is released from the sarcoplasmic reticulum, and this gives a positive inotropic effect (higher contractility).

Mechanism of Positive Inotropic Action



Digitalis toxicity

- Digitalis toxicity can be caused by high levels of digitalis in the body or a decreased tolerance to the drug.
- Patients with decreased tolerance may have "normal" digitalis levels in their blood.
- Risk factors
- 1-Cardiac diseases
- 2-Reduced kidney function will cause digitalis to build up in the body rather than be removed normally through urine.
- 3-metabolic factors: Hypokalemia, hypernatremia, hypercalcemia, acid-base imbalance.

- Digoxin toxicity causes hyperkalemia, or high potassium. The sodium/potassium ATPase pump normally causes sodium to leave cells and potassium to enter cells. Blocking this mechanism results in higher serum potassium levels.
- In states of hypokalemia, or low potassium, digoxin toxicity is actually worsened because digoxin normally binds to the ATPase pump on the same site as potassium. When potassium levels are low, digoxin can more easily bind to the ATPase pump.
- Magnesium deficiency will develop digoxin toxicity at relatively low serum concentrations because Magnesium is an essential co-factor for the sodium-potassium ATPase.

- ***4-Taking medications that interact with digitalis*** such as:
- Quinidine/the serum digoxin doubles during treatment with therapeutic doses of quinidine. Almost every patient treated with quinidine will have a decrease in the renal clearance of digoxin and many will have a decrease in the volume of distribution of digoxin, same as with verapamil, amiodarone both increase serum concentration of digoxin .

- Thiazide and Loop diuretics – cause hypokalemia which increases the toxicity
- Spironolactone – increases half life of digoxin
- Cortisone – Na retention and K loss
- Erythromycin increases the bioavailability of digoxin.
- Diagnosis
- ECG is important to check irregular heartbeats.
- Blood tests: BUN and creatinine (which help reveal kidney function)
- Digoxin and digitoxin levels
- Potassium & Magnesium levels

Toxicity features

- ***Cardiac:*** Digitalis poisoning can cause heart block and either *Brady-cardiac arrhythmia* or tachycardia *arrhythmia or both*, depending on the dose and the condition of one's heart.
- Younger persons without significant heart disease may develop bradyarrhythmia and heart block.
- AV block and severe bradycardia mediated by increased vagal activity (sympathetic stimulation).

- ***Neurological:*** confusion, drowsiness, dizziness, insomnia, nightmares, agitation, depression, psychosis, delirium, amnesia, and convulsions.
- ***Ophthalmic:*** disturbance of color vision (mostly yellow and green color) called xanthopsia, Other oculotoxic effects of digoxin include seeing a "halo" around each point of light.
- ***Gastrointestinal:*** loss of appetite, nausea , vomiting, and diarrhea as the gastrointestinal motility increase

Cardiac arrest and death can occur from ventricular fibrillation, ventricular tachycardia and severe bradyarrhythmias.

Neurological symptoms including altered mental status can occur, even without hypoperfusion of the brain. Ocular manifestations include xanthopsia, or seeing yellow.

Most experts believe that the famous artist Vincent van Gogh was using foxglove, the flower from which digoxin is derived, which could explain the yellow paintings toward the end of his life. Here are two examples — one a self-portrait, the other a street scene.

Management of poisoning

1. Stop further absorption & increase the removal of unabsorbed digitalis.

- Induced emesis with *ipecac syrup* is not recommended because of the increased vagal effect and can worsen slow heart rhythms.
- *Gastric lavage* is useful after ingestion because of the prolonged absorption of digoxin.

- Activated charcoal is indicated for acute overdose or accidental ingestion, blood levels may be lowered with repeated doses of charcoal, given after gastric lavage.
- Steroid-binding resins, such as cholestyramine and colestipol, can prevent the further absorption of digoxin. These agents are especially effective in patients with chronic toxicity and/or significant renal insufficiency.

2. Reversal of arrhythmias

- Bradyarrhythmias that are hemodynamically stable may be treated with observation and discontinuation of the drug. Ensure proper hydration to optimize renal clearance of excess drug.
- *Atropine* may be useful in blocking digoxin-induced effects of enhanced vagal tone on the sinoatrial (SA) and atrioventricular (AV) nodes.
- Short-acting beta blockers (eg, esmolol).
- Phenytoin and lidocaine are useful antiarrhythmics for the treatment of digoxin toxicity if Fab fragments are ineffective or unavailable..

3. Correct electrolyte abnormalities

- In acute settings, hyperkalemia is more common, while in chronic intoxication, hypokalemia and hypomagnesaemia are common.
- Treat hyperkalemia when the K+ level is greater than 5.5 mEq/L. Standard treatment for hyperkalemia, including bicarbonate, dextrose, and insulin(Facilitates the uptake of glucose into the cell, which results in an intracellular shift of potassium)
- Calcium is not recommended to treat hyperkalemia in this setting, because ventricular tachycardia or ventricular fibrillation may be precipitated. This is based on the fact that intracellular calcium levels are already high in the setting of digoxin toxicity.
- Potassium supplementation is generally recommended in the setting of hypokalemia (K+< 3meq/L) and AV block.

- Correct *hypomagnesemia*. **IV magnesium sulfate**, 2 g over 5 minutes, has been shown to terminate digoxin-toxic cardiac arrhythmias.
- After an initial bolus of 2 g intravenously, a maintenance infusion at 1-2 g/h is initiated. Monitor magnesium levels approximately every 2 hours. The therapeutic goal is a level between 4 and 5 mEq/L.

- *Forced diuresis* is not recommended because it has not been shown to increase renal excretion and can worsen electrolyte abnormalities.
- *Hemoperfusion and hemodialysis* ineffective due to high molecular weight and increased volume of distribution.

- **Digoxin Immune Fab (Ovine)** is the generic name for an antidote for overdose of digitalis. It is made from immunoglobulin fragments from sheep who have already been immunized with a digoxin derivative.
- Production of antibodies specific for digoxin involves conjugation of digoxin as a hapten to human albumin.

- DigiFab has an affinity for digoxin greater than the affinity of digoxin for its sodium pump receptor.
- When administered to the intoxicated patient, DigiFab binds to molecules of digoxin reducing free digoxin levels, which results in a shift in the equilibrium away from binding to the receptors, thereby reducing cardio-toxic effects.
- Fab-digoxin complexes are then cleared by the kidney.

Indications for digibind

- • Serum digoxin level > (10 ng/mL) in acute ingestion
- or acute ingestion of > 10 mg in adult, 4mg in children
- Serum potassium > 5.0 mEq/dL) in acute ingestion
- • Chronic ingestions causing steady-state serum digoxin concentrations exceeding 6 ng/mL in adults or 4 ng/mL in children
- • Life threatening cardio toxicity:
- • Ventricular dysrhythmia
- • Progressive bradycardia

- **Each vial of DigiFab contains**
- **[40 mg of digoxin immune Fab, which will bind approximately to 0.6 mg digoxin or digitoxin, is intended for intravenous administration after reconstitution with 4 mL of Sterile Water for Injection USP.**

- $$\text{Dose} = \frac{(\text{SDC}) \cdot \text{Vd} \cdot (\text{weight in kg})}{1000}$$

SDC : Serum Digitalis Concentration in ng/mL

Vd : mean volume of distribution,

For digoxin = 5.6 L/Kg, digitoxin = 0.65 L/Kg

ADVERSE REACTIONS

- Exacerbation of low cardiac output states and congestive heart failure due to the withdrawal of inotropic effect of digitalis.
- Hypokalemia due to reactivation of the sodium-potassium ATPase
- Rare allergic reactions, Patients with a history of allergy, especially to antibiotics, appear to be at particular risk

- Case study
- A 65-year-old woman was admitted to emergency after ingestion of 70 tabs of digioxin (0.0625 mg)in a suicide attempt, 5 hrs. previously, she underwent lavage and received a slurry of AC, lab analysis included serum K 4.3 mmol/L, serum digoxin 15.5 ng/ml, HR 130 beats/min and irregular, patient was nauseated and vomited, her vision was blurred, after several hrs. her serum K was 5mmol/l. ttt phenytoin 500mg, 400mg of digoxin immune fab over 30 min was administered.