CLINICAL TOXICOLOGY LAB.

5TH STAGE / 1ST SEMESTER

(2021 – 2022)

CLINICAL TOXICITY OF DIGITALIS (PART I)

ASSIS. LECTURER

ZEENA A. HUSSEIN

NIBRAS J. TAHSEEN

INTRODUCTION & BACKGROUND:

- A group of naturally occurring and pharmacologically active compounds, that belong to cardiac glycosides
- They are extracted from the leaves of Foxglove plant (*Digitalis purpurea*)
- The most common known active forms are: (digoxin & digitoxin)
- Other preparations available internationally include digitoxin, ouabain, lanatoside C, deslanoside, and gitaline
- 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, & could be used in patients with poor or erratic kidney function.

PHARMACOKINETIC DIFFERENCES BETWEEN DIGOXIN & DIGITOXIN:

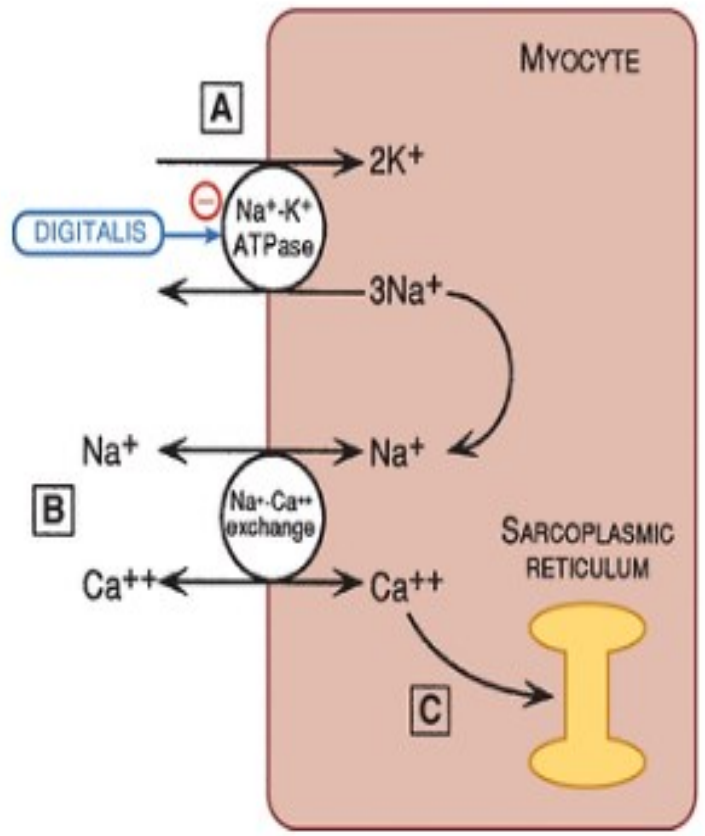
Measurements	digoxin	digitoxin
Onset time	1.5 – 6 hr	3-6 hr
peak	4-6 hr	6-12 hr
T 0.5	31-40 hr	4-6 days
Protein binding	20-25 %	90-97%
Vd	7-8L/kg	0.6L/Kg
Excretion route	Renal 75%	Hepatic 80%
Toxic blood level	2.4 ng/mL	over 30 ng/mL

Formulations:

- Injection (IV; rarely used IM)
- Oral Solution
- Tablets

MECHANISM OF ACTION: (POSITIVE INOTROPIC)

- Digitalis binds to and inactivates the Na+/K+-ATPase pumps in the plasma membrane of myocardial cells, producing a rise in the cytoplasmic Na+ concentration
- 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 exchanger 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).

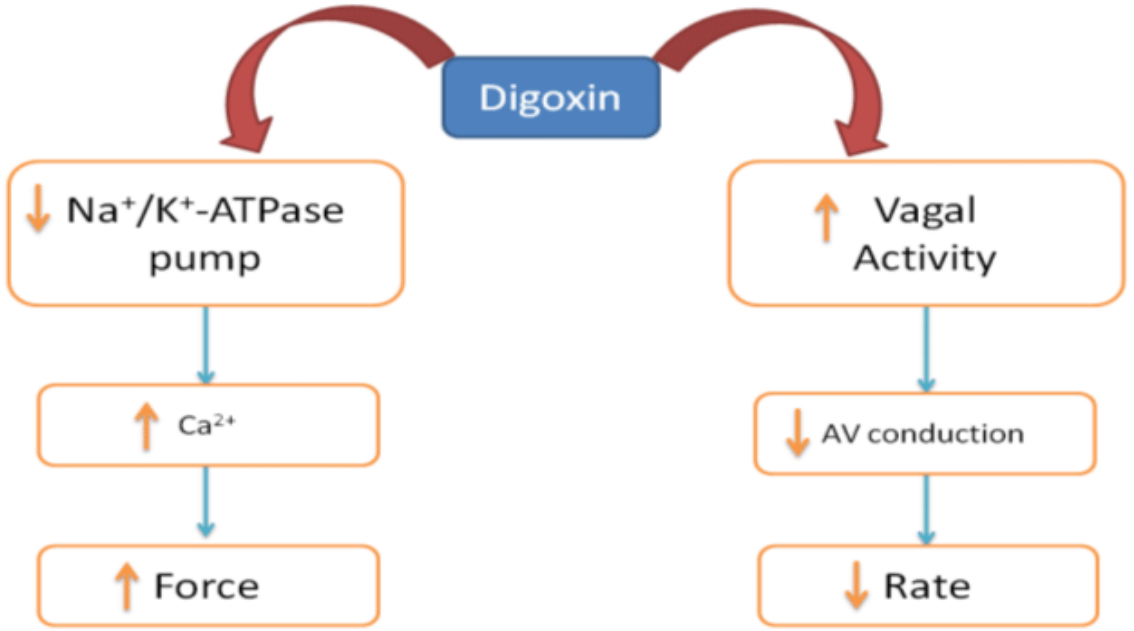


- Also, digoxin has a direct effect on vagal nerve activity, increasing vagal nerve outflow, leading to decreased AV conduction and rate (this may explain the bradycardia and AV block occurring with toxicity)

Therapeutic Role

Atrial fibrillation

Chronic heart failure



DIGITALIS TOXICITY & RISK FACTORS:

- 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 that predisposes to digitalis toxicity may include:
  - Age
  - Impaired renal function or CKD
  - Electrolyte imbalance
  - Drug-drug interactions like:
    1. Quinidine >>> increases serum level of digoxin
    2. Thiazide and loop diuretics >>> increase toxicity
    3. Spironolactone >>> increase half life of digoxin
    4. Corticosteroids >>> may increase toxicity
    5. Erythromycin >>> increase bioavailability

IMPORTANT NOTES:

- Digoxin toxicity causes hyperkalemia, or high potassium (why?)
  - 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 (why?)
  - 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.
- Quinidine increases serum concentration of digoxin (why?)
  - Because quinidine competes with digoxin for protein binding, and displacing digoxin from protein binding >>> thus increasing free serum level

IMPORTANT NOTES:

- Hypercalcemia increases toxicity with digoxin (why?)
  - Digoxin enhances Ca+2 absorption into cardiac myocytes, which is one of the ways it increases inotropy. This can also lead to Ca+2 overload and increased susceptibility to digitalis-induced arrhythmias
- Verapamil increases serum concentration of digoxin (why?)
  - It alters renal elimination of digoxin by competing for tubular secretion

TOXIC FEATURES OF DIGOXIN:

- **Signs & symptoms of acute toxicity:**

Cardiac

sinus bradycardia, second or third degree AV block. Any type of dysrhythmia is possible

Neurological

confusion, weakness, lethargy

Gastrointestinal

nausea, vomiting, abdominal pain

Electrolyte

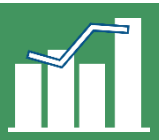
Hyperkalemia
(> 5.5 mEq/L is a poor prognostic sign)

- **Sins & symptoms of chronic toxicity:**

Gastrointestinal	Neurological	Visual
Patients may have more subtle signs of acute digoxin toxicity (nausea, anorexia)	confusion, drowsiness, headache, hallucinations	sensitivity to light, yellow halos around lights, blurred vision

Cardiac	Electrolyte
bradydysrhythmias (often unresponsive to atropine) ventricular tachydysrhythmias	hyperkalemia (sometimes hypokalemia especially if diuretics are used)

DIAGNOSIS OF DIGOXIN TOXICITY:

- History 
- Signs and symptoms 
- EKG 
- Digoxin levels 
- Electrolytes 

- **History:**
  - Include all risk factors that may predispose to digoxin toxicity
- **Clinical signs & symptoms (for acute or chronic toxicity)**
- **EKG analysis:**
  - Almost any arrhythmia or conduction abnormality may be seen with digitalis toxicity
- **Digoxin level:**
  - An initial 4-6 hour post-ingestion level is appropriate.
  - Therapeutic range of digoxin is 0.5 - 1.0 ng/mL
  - Toxicity begins >2.0 ng/mL
- **Electrolytes (K+, Ca+2, Mg+)**
  - Hyperkalemia >>> a level of K+ as high as 5.5 mEq/L is associated with poor prognosis
  - Hypokalemia >>> Can predispose the patient to further dysrhythmias and should be corrected with close monitoring to avoid hyperkalemia. Goal Potassium level 4.0 mEq/L - 5.0 mEq/L
  - Hypomagnesemia may cause refractory hypokalemia
  - Hypercalcemia >>> causes excessive arrythmias