Digitalis toxicity

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2014

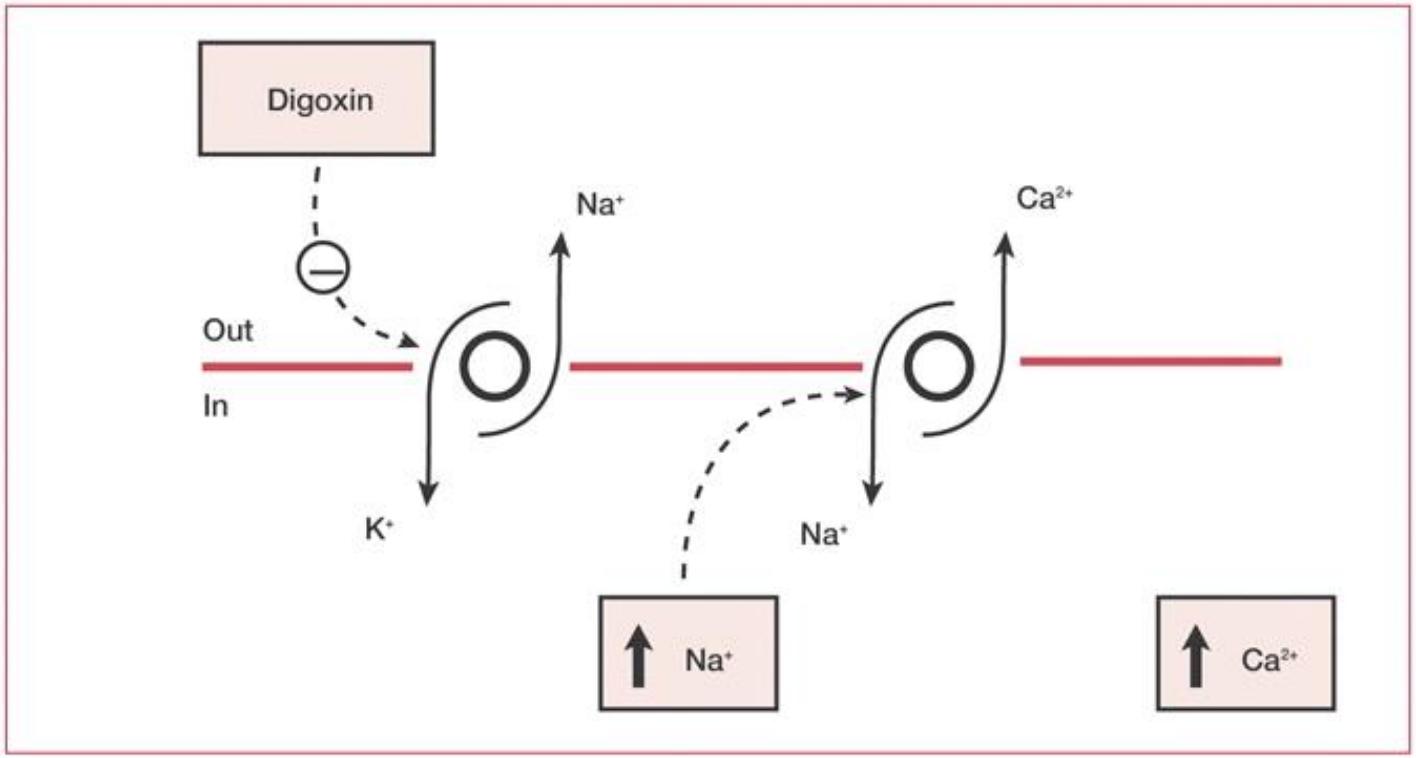
Cardiac glycosides

- Digitalis is the oldest compound in cardiovascular medicine
- Cardiac glycosides include digoxin, digitoxin, digitalis and ouabain
- +ve inotropic, -ve chronotropic
- Heart failure, Atrial fibrillation, Atrial flutter
- Low TI

Mechanism Of Pharmacological Action

- Potent inhibitors of cellular Na+/K+-ATPase
  - This ion transport system moves 3 sodium ions out of the cell and brings 2 potassium ions into the cell
  - Necessary for cell survival
  - Subsequent inhibit the Na+-Ca++ exchanger
    - Three sodium ions are exchanged for each calcium
    - An increase in intracellular sodium concentration competes for calcium through this exchange mechanism leading to an increase in intracellular calcium concentration, leading to **increases contractility (inotropy)**
- Increase vagal efferent activity to the heart, reduces sinoatrial firing rate (decreases heart rate; **negative chronotropy**) and reduces conduction velocity of electrical impulses through the atrioventricular node (**negative dromotropy**)

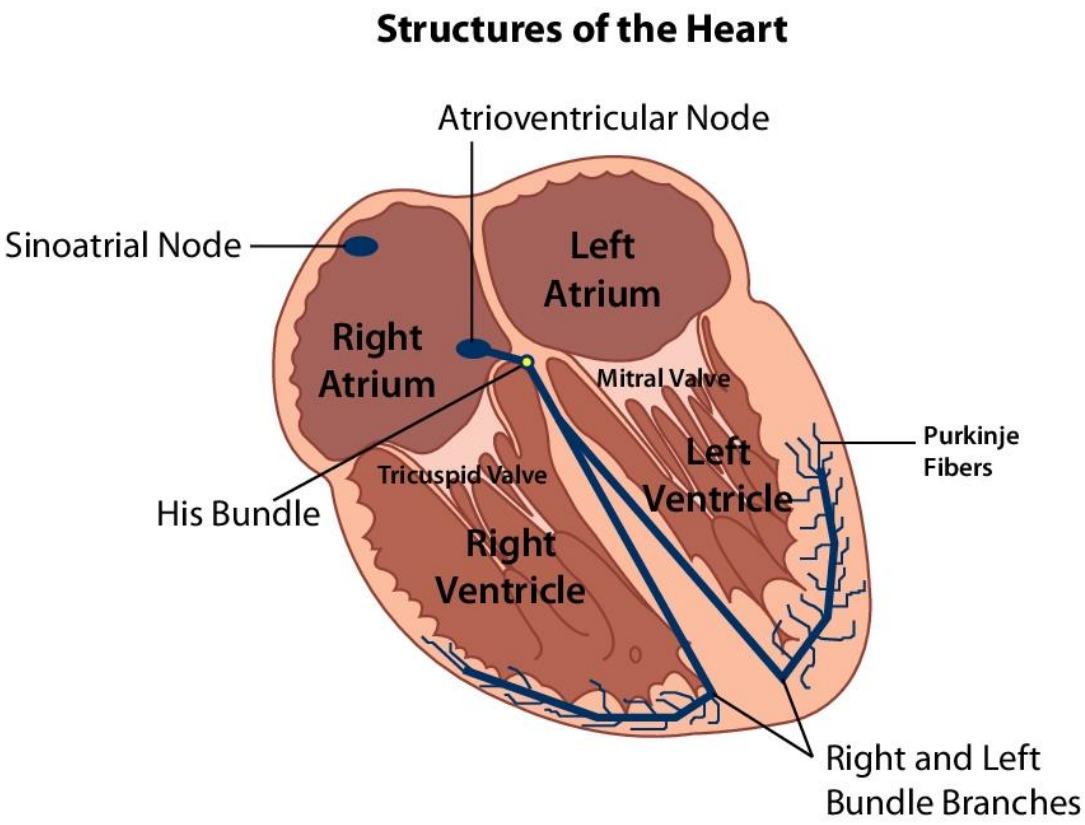
Mechanism Of Pharmacological Action

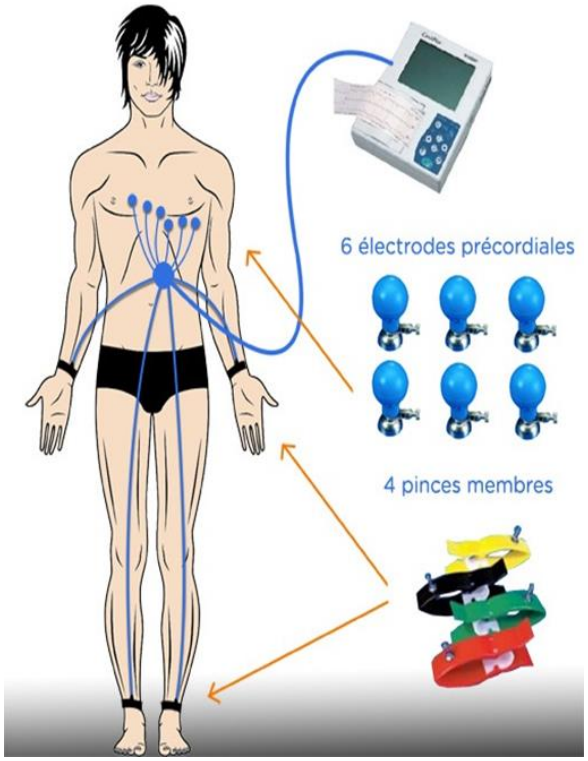


Kinetics

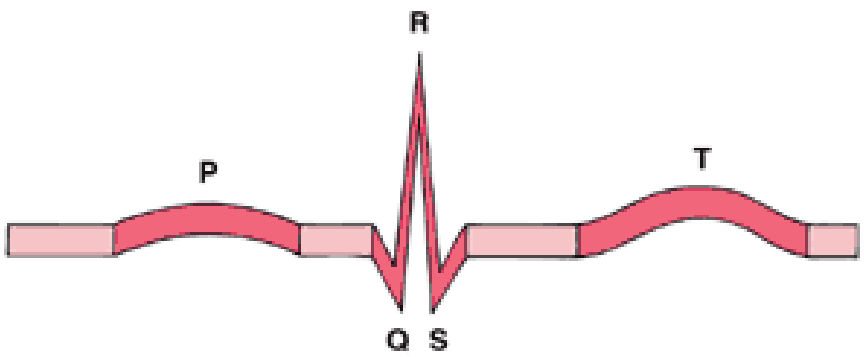
Volume of Distribution	Protein Binding	Half Life	Time to peak (serum)
5-7 L/kg	25%	Age, Renal, and cardiac function dependent Approximately 38 Hours (parent drug)	Oral: 1-3 hours Distribution phase: 6-8 hours Steady state: 7-10 Days

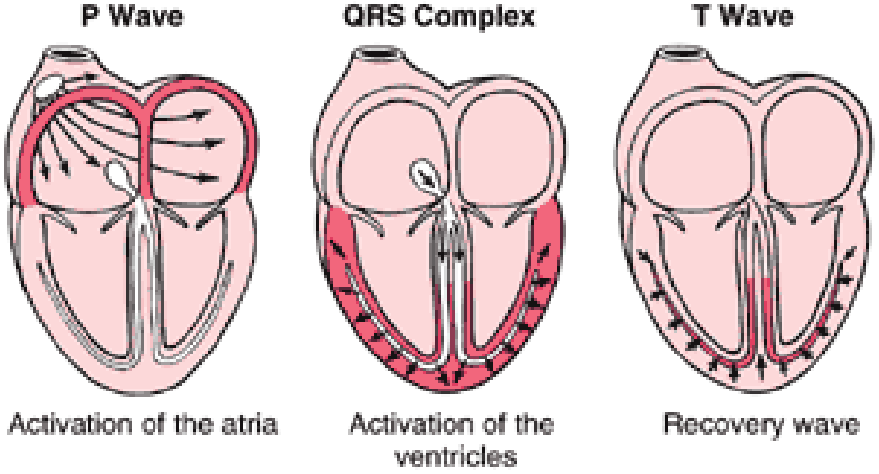
Electrocardiography (ECG)

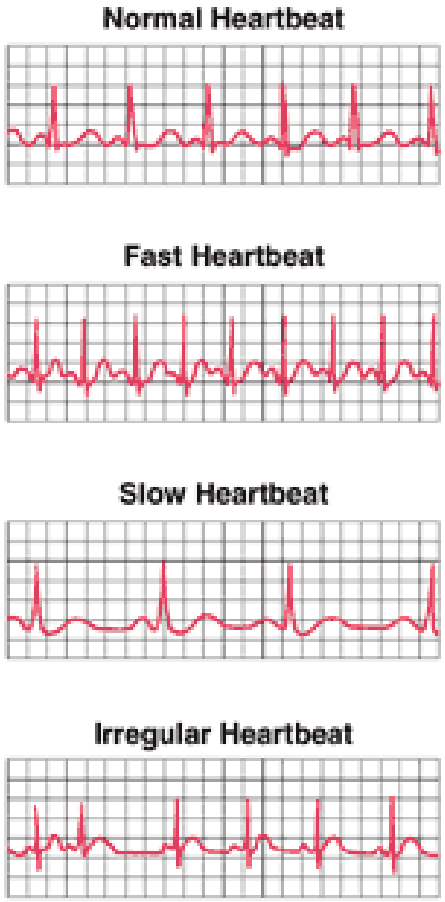




ECG


R
P
T
Q S


P Wave
QRS Complex
T Wave
Activation of the atria
Activation of the ventricles
Recovery wave


Normal Heartbeat
Fast Heartbeat
Slow Heartbeat
Irregular Heartbeat

Digitalis toxicity

- life-threatening condition, 1,500/year
- In 2011, there were 2,513 cases involving cardiac glycosides reported to U.S. poison control centers. Of these, 90 experienced major effects (i.e, life threatening resulting in prolonged hospitalization) and 26 died
- Low TI
  - Therapeutic levels are 0.6 to 2 ng/mL
  - levels of toxicity between therapeutic and toxic ranges
- Acute toxicity
  - cardiac effects
  - nausea and vomiting
- Chronic toxicity
  - cardiac effects
  - nonspecific symptoms include fatigue, malaise, and visual disturbances

Digitalis toxicity

- Causes
  - High levels of digitalis in the body (over dose)
  - Accumulation during chronic treatment
  - Decreased tolerance to the drug, have normal levels of digitalis in blood
- Risk factors
  - Electrolyte Imbalance
    - Potassium loss (thiazide)
    - Low levels of magnesium
    - Hypercalcemia
  - Quinidine, flecainide, verapamil, amiodarone.
  - Kidney failure and dehydration

Signs/symptoms of acute toxicity

Gastrointestinal

nausea, vomiting, abdominal pain

Neurological

weakness, confusion, Photophobia

Electrolyte

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

Cardiac

Palpitations, bradycardia, heart block, several types of arrhythmias, and Shortness of breath

Signs/symptoms of chronic toxicity

Gastrointestinal

Less than that of acute digoxin toxicity (nausea, anorexia)

Neurological

confusion, drowsiness, headache, hallucinations

Visual

sensitivity to light, yellow halos around lights, blurred vision

Diagnosis

- Serum digoxin level
- Electrolytes
- Renal function studies
- ECG

Diagnosis

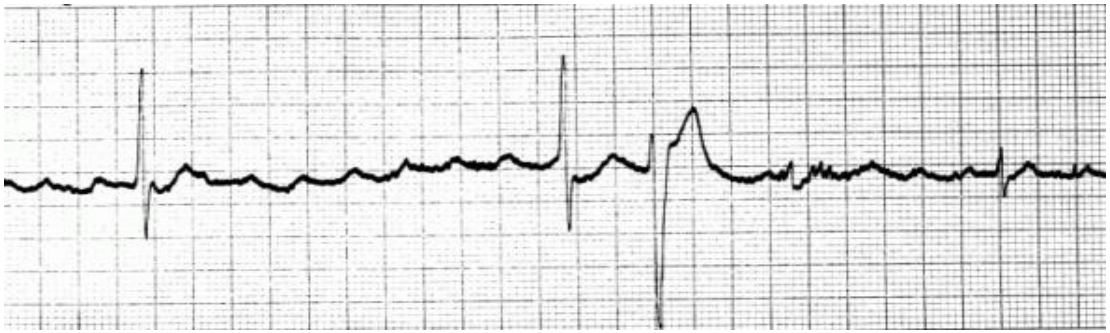
- Serum digoxin level
  - Toxicity begins >2.0 ng/mL
  - May be misleading in the acutely poisoned patient
  - False-negative assay results may occur with acute ingestion of non-digoxin cardiac glycosides (eg, foxglove or oleander)
  - Digoxin's long distribution phase results in high serum levels for 6-10 hours prior to completed tissue distribution

Diagnosis

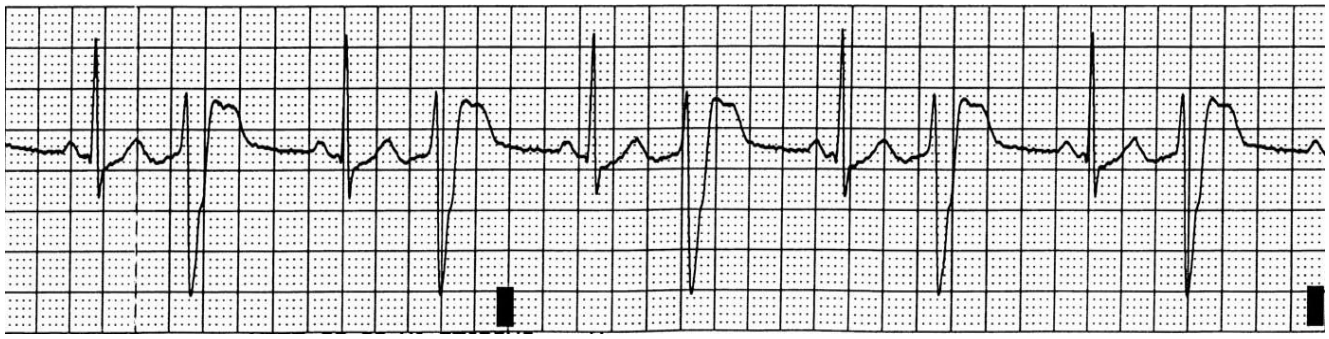
- Electrolytes
  - Hyperkalemia
  - Chronic toxicity: hypokalemia and hypomagnesemia
- Kidney function tests
  - BUN
  - Creatinine

Diagnosis

- ECG
  - May cause almost any dysrhythmia
    - atrial tachycardia with a 2:1 conduction
    - bidirectional ventricular tachycardia
    - atrial fibrillation with a slow ventricular response



atrial tachycardia with block



Sinus rhythm with frequent PVCs in a pattern of ventricular bigeminy

Treatments

Decontamination/enhanced elimination

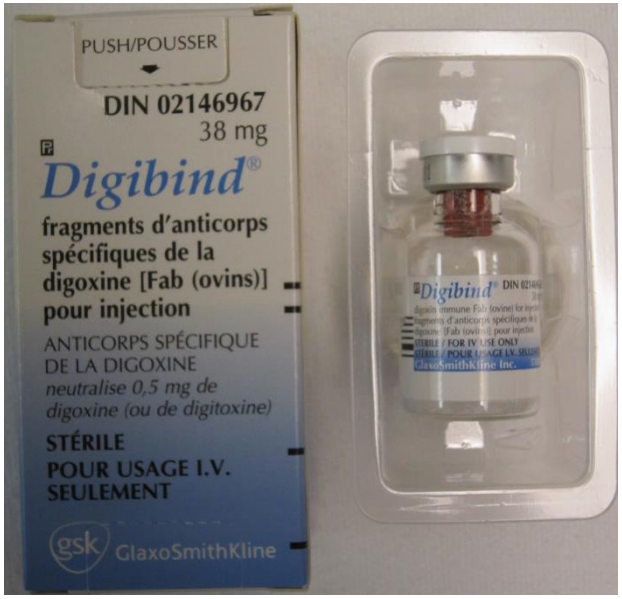
For acute overdose: Activated charcoal, multiple dose activated charcoal, gastric lavage

Enhanced elimination (dialysis, hemoperfusion) does not effectively remove digoxin due to large volume of distribution and relatively high protein binding

Treatments

Digoxin immune Fab (ovine)

- Antidote, highly effective in treating life-threatening signs of digoxin toxicity such as hyperkalemia, hemodynamic instability, and arrhythmias
- Primary treatment of digoxin toxicity
- Indications:
  - Ingestion of 10 mg of digitalis (in children, 4 mg)
  - Serum digoxin level greater than 8 ng/mL in adults at steady state
  - Hyperkalemia (greater than 5 mEq/L)
  - Altered mental status
  - Rapidly progressive signs and symptoms of toxicity



Treatments

- DigiFab (40 mg of Fab), binds 0.5 mg digoxin
- 30 minute slow IV infusion
- Acute ingestion of unknown amounts and serum concentration of digoxin:
  - 20 vials of Digoxin immune fab (ovine)
  - Can split dose into 10 vials followed by another 10 vials to avoid a febrile reaction
- Chronic ingestion unknown serum digoxin concentration
  - 6 Vials of Digoxin immune fab (ovine) in adults and Children > 20 Kg
  - 1 Vial of Digoxin immune fab (ovine) in infants and Children < 20 Kg

Treatments

For known amounts of digoxin

Dose In Vials = **Digoxin ingested (mg) X 1.6**

Round up to the nearest vial

Treatments

For known digoxin serum concentration

$$\text{Dose In Vials} = \frac{\text{(Serum Digoxin ng/mL) x Weight (kg)}}{100}$$

Round up to the nearest vial

Treatments

Digoxin immune Fab

- Adverse Effects
  - Digitalis withdrawal: exacerbation of HF, rapid ventricular response and postural hypotension
  - Hypokalemia
  - Phlebitis
  - Fever, May occur with doses above 10 vials
- Warning
  - Patients who require digoxin's inotropic action may deteriorate secondary to the withdrawal of digoxin
  - Additional inotropic support may be required for these patients (e.g, dopamine, dobutamine or vasodilators)

Treatments

Electrolyte imbalance

- Hyperkalemia, use insulin plus glucose, and sodium bicarbonate if the patient is acidotic
- Hemodialysis may be necessary for uncontrolled hyperkalemia
- Correct hypokalemia (usually in chronic intoxication)
- Concomitant hypomagnesemia may result in refractory hypokalemia

Dysrhythmias

- Short-acting beta blockers (eg, esmolol) may be helpful for supraventricular tachyarrhythmias with rapid ventricular rates, but may precipitate advanced or complete AV block
- Phenytoin and lidocaine are useful for ventricular tachycardia
- Phenytoin can suppress digitalis-induced tachydysrhythmias
- Atropine has proved helpful in reversing severe sinus bradycardia
- Magnesium sulfate may terminate dysrhythmias

Digoxin Toxicity: Case Study

76 year old woman with history of atrial fibrillation, hypertension, renal impairment, breast cancer, osteoarthritis. Stroke 1 month prior to admission.

Medications: digoxin 250 mcg once daily, amlodipine, lisinopril, indapamide
SR, simvastatin, clopidogrel, bisoprolol, omeprazole, erythromycin

Presents with nausea, vomiting, change in vision, lethargy

VS: BP "normal"; HR 35-38 bpm

Labs

Digoxin levels: prior to admission: 3.4 ng/mL (0.8-2 ng/mL normal range for this lab)	On admission: 2.9 ng/mL	Increased digoxin dose from 125 mcg/day to 250 mcg/day 28 days ago

Digoxin Toxicity: Case Study

Summary: elderly patient with renal impairment, signs/symptoms of (chronic) digoxin poisoning with elevated digoxin level

Potential drug interactions:

Amlodipine	Bisoprolol	Erythromycin
(Ca^{+2} channel blocker) can increase digoxin level and enhance digoxin AV blocking effect	(ß blocker) can enhance digoxin's bradycardic effect	(macrolide antibiotic) can increase digoxin level

Digoxin Toxicity: Case Study

Received digoxin-specific antibody fragments (Fab)

Weight 108 kg

Digoxin level: 2.9 ng/mL

Fab Dose In Vials = $\frac{\text{(Serum Digoxin ng/mL) x (Weight in kg)}}{100}$

3 vials administered

Digoxin Toxicity: Case Study

6 hours post digoxin Fab infusion: digoxin 1.9 ng/mL

At discharge (91 hours post digoxin Fab infusion): digoxin 1 ng/mL, HR 65 bpm, digoxin toxicity signs/symptoms resolved

Monitoring

HR: improved (35-38 bpm to 65 bpm at discharge)	BP: remained stable	EKG: unchanged from baseline (atrial fibrillation)	K^+ not provided in this report (although this was a chronic toxicity not acute)

Digoxin Toxicity: Case Study

Approaches to digoxin poisoning in the chronically poisoned patient will depend on the status of the patient (signs/symptoms, age, renal function, cardiac status)

This was an elderly patient with impaired renal function who clearly had digoxin toxicity and an elevated level.

The clinical decision was made to treat promptly with digoxin Fab rather than prolong her clinical course.


Thank
You!