Digitalis Glycosides

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pharmacology

Heart Failure
Increasing prevalence , Most often following CAD

1. S/S of volume overload
   SOB
   peripheral edema
   Pulmonary edema
2. Cardiac output
   Exercise tolerance
   muscle fatigue
3. Cardiomegaly
4. Tachycardia

TREATMENT GOALS –
   Decrease mortality
   Decrease symptoms and increase functional status
Heart Failure

- Diastolic 'eg
  - Cardiomegaly
  - Normal EF
  - No response to inotropes

- Systolic
  - EF below 45%
  - Eg Post MIo responsive to inotropes

S/S of NEUROHUMORAL COMPENSATION - tachycardia, SOB, edema (lung, periphery), exercise tolerance

- Sympathetic
  - Increase Force (preload)
  - Increase Rate (preload)
  - Increase Venous tone (preload)
  - Increase Peripheral resistance (afterload)

- Increase CO

- Downregulation of β1 Cardioreceptors

- INOTROPY decrease

- Renin
  - RBF decrease
  - AG II increase
  - Aldosterone increase (afterload)
  - Hypertrophy- initial high CO

- Ischemic changes

- Impaired filling

- remodeling

- EF decrease and apoptosis

Myopathy

- Low cardiac efficiency

- Decreased inotropy

- Low tissue perfusion

- Periheral tissue anoxia

- RBF
  - Renin
  - Angiotensin
  - Aldosterone

- Blood volume
  - Pre-load
  - Poor renal function
  - Cardiac dilatation
  - ANF
  - Saluresis

- Myocardial dysfunction

- Cardiac output

- Renal perfusion

COMPENSATION
1. normal curve - representing 10 mm Hg filling pressure and normal stroke volume,
2. depressed - representing higher filling pressure to achieve equal amounts of stroke volume, which can be observed in cases of diastolic heart failure
3. positive inotropic agent- more stroke volume can be ejected with similar filling pressures (contractile forces, which are delivered by the force-velocity relation of contractility), which can be the result of positive inotropic drugs like digitalis.

Principles of treatment

Four determinants of cardiac function

1. Pre-load - SFD, Diuretics, Venodilators
2. After-load – reduction of arteriolar tone and combat endothelin
3. Contractility – Inotropes
4. Heart rate - Beta blockers to reduce compensatory sympathetic tone
Cardiac glycosides

• Plant source- foxglove, squill, oleander, Lily of the valley
• Three components
  – A steroid ring
  – A lactone
  – Sugar residues

Digitalis mode of action
Digitalis mode of action

By inhibiting Na\(^+\)/K\(^+\)-ATPase, cardiac glycosides increase intracellular sodium concentration. This leads to accumulation of Ca\(_i\) via the Na\(^+\)-Ca\(^{2+}\) exchange system. Increased Ca\(_i\) causes more calcium to be released by the sarcoplasmic reticulum, making more calcium available to bind to troponin-C, which increases contractility (inotropy).

Inotropy

- Na and Ca enter cardiac muscle in membrane depolarisation
- Triggers Ca release from SR and intracellular Ca
- Combines with Troponin C-Xlinking of Ac-Myosin
- Na extrusion by Na-K ATPase; Ca pushed into SR, bound to Calsequestran OR extruded by Na-Ca exchanger
- B agonists and PDE inhibitors - cAMP -PKA- open L Ca Channels - Ca enters cell.
**Electrical effects of digitalis**

- Shortening of the AP (Ca i and K i)
- Shortened RP of the atria and ventricles
- Increase depolarisation (Na i)
- Resting membrane potential decrease
- Slope of phase 4 increase
- Depolarising after potentials
- ECTOPICS

**Clinical implications of electrical changes**

- Intracellular Na, Ca and K changes - toxicity
- Generate after potentials
- Affects steepness of phase 4 slope
- Rapid depolarisations
  - ECTOPICS
    - Pulsus Bigeminus, Trigeminus, Arrhythmias and Fibrillation
## Electrical effects

### Direct effects
- a. briefly prolonged AP followed by protracted shortening (Ca and K conductance)
- b. resting membrane potential falls
- c. oscillatory depolarisations become ECTOPICS
  
  Ectopics sustained in Purkinje fibres

### Indirect effects – PARASYMPATHOMIMETIC
- a. Atropine block at low doses
- b. muscarinic transmission in myocytes and central vagus nucleus
- c. AV node affected - rich innervation
- d. Toxicity
  - a. AV junctional rhythms
  - b. Premature vent depolarisations
  - c. Vent tachycardias
Cellular effects

- Na-K-ATPase inhibition – Na increase (K control)
- Na – Ca exchanger disruption - increase
- LVOC Ca channels open
- High Ca concentrations
- Sarcoplasmic Ca release

Toxicity is therefore a function of electrolyte concentrations of K and Ca

Indirect effects

1. Vagal stimulation
   - Central
   - baroreceptors (aorta arch)
   - muscarinic cardiac receptors
   - Decreased heart rate
   - Decreased AV conduction
   - Prolonged RP of AV node
     - HEART BLOCK
2. Sympathetic tone decreased
   - BRADYCARDIA
ECG effects

• Prolonged PR interval
• P waves – premature beats, flutter, fibrillation
• II- III degree heart block
• Ventricular arrhythmias
• ST depression ; T wave inversion

Digitalisation

Aim
Quick steady state level required

Initial loading dose
3-4 doses 6-8 hrly /24 hours
Followed by
MAINTENANCE DOSE
Dose excreted daily (approx) 0.25 mg/day
Chief cardiac glycosides

<table>
<thead>
<tr>
<th>KINETICS</th>
<th>DIGOXIN</th>
<th>DIGITOXIN</th>
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<tbody>
<tr>
<td>Absorption</td>
<td>60-85%</td>
<td>90-100%</td>
</tr>
<tr>
<td></td>
<td>15-30 mts</td>
<td>25-120 mts</td>
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<tr>
<td>Time-peak</td>
<td>1.5-5 hrs</td>
<td>4-12 hrs</td>
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<tr>
<td>Half-life</td>
<td>36 hrs</td>
<td>4-6 days</td>
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<tr>
<td>Protein binding</td>
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<td>90%</td>
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<tr>
<td>Digitalising dose</td>
<td>1.25-1.5</td>
<td>0.7-1.2</td>
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<tr>
<td>Maintenance dose</td>
<td>0.25-0.5 mg</td>
<td>1.0 mg</td>
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<tr>
<td>Metabolism</td>
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<td>Hepatic (&gt;80%)</td>
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<tr>
<td>Excretion</td>
<td>Renal</td>
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<tr>
<td>Vd</td>
<td>7L/Kg</td>
<td>0.6L/Kg</td>
</tr>
</tbody>
</table>

dosing

- Once/day even in mild renal impairment
- Steady state in approx 1 week of maintenance dosing
- 3-4 doses for digitalisation
- Oral digoxin well absorbed
- Never by i.m. route
Indications

• Failure
  - LVF
  - CCF
  PAT
    supraventricular
    flutter
    fibrillation

Toxicity / Interactions/Disease states

• GIT – nausea, vomiting
• Cardiac
  — Bradycardia, ventricular tachycardias
• CNS
  — Hallucinations, delirium, vision
• Metabolic disturbances
• Diuretics, Verapamil, Quinidine
• Sympathetic amines
• Thyroid disorders, renal failure