Q5 Outline the kinetic characteristics and the mode of action of digoxin. (75% of marks) List the cardiovascular effects of digoxin (25% of marks) (Sept 2009)

Digoxin - a cardiac glycoside derived from the digitalis plant, used in the management of arrhythmias and cardiac failure

PHARMACEUTICAL

Presented as oral tablets (from 62.5mcg to 250mcg strength) and an IV formulation (various strengths). Narrow therapeutic range (usually aim levels <0.8-1.2mcg/L) and broad side effect profile

PHARMACODYNAMICS

MECHANISM - direct action is via inhibition of Na/K ATPase, resulting in increased intracellular Na concentrations. This affects the Na/Ca exchanger and results in an increase in intracellular Ca, which is sequestered in the SR and released with the AP resulting in increased force of contraction. Reduction in intracellular K reduces conduction through the AV node. Indirect effects include release of ACh at cardiac muscarinic receptors resulting in bradycardia, and further increase in the refractory period of the AV node. The slowing in conduction improves tachyarrhythmias and allows for more coronary artery filling time, LV filling, and improved LV output.

SIDE EFFECTS

CVS - arrhythmias, conduction block (prolonged QRS/PR/QT).
GIT - anorexia, N/V, weight loss
CNS - malaise, fatigue, headache, visual changes (red/green colour), confusion
Drug interactions - thyroxine can increase V_D and renal clearance; beta and Ca channel blockers can decrease conduction.
Needs regular drug levels. Specific antidote available if poisoning occurs 'Digibind'.

PHARMACOKINETICS

ABSORPTION

Route - PO or IV (IM associated with tissue necrosis)
Dose - loading up to 1mg over 24 hours then 62.5-125mcg daily
Bioavailability - 60-80% (note 10% of general population harbours the enteric bacterium Eubacterium lentum, which converts digoxin to an inactive metabolite)
Time to onset - 1-2 hours PO, minutes IV

DISTRIBUTION

Volume of distribution 5-11L/kg. Principle reservoir skeletal muscle (hence dose based on lean muscle mass)
Protein binding - 25%
Lipid solubility - high

METABOLISM

Sugar sequences hydrolysed in gut, removal of lactone ring by gut bacteria, most of drug excreted unchanged

ELIMINATION

Mostly excreted in urine unchanged, half life 36-48 hrs

CARDIOVASCULAR EFFECTS

- Increase in intracellular Ca leads to increased inotropy
- Decrease in intracellular K levels causes hyperpolarization and slows conduction velocity through the AV node, reducing heart rate. It also prolongs phase 3 and 4 of the ventricular action potential, prolonging the refractory period and the PR and QT intervals.
- Altered autonomic activity contributes to the reduction in HR as well as reduced vascular resistance and venous tone in patients with cardiac failure
- The reduction in heart rate increases diastolic time, increases LV filling and coronary blood supply.
- Improvement in preload, contractility and myocardial oxygen supply improves cardiac output