Q10 Compare and contrast the mechanism of action, pharmacokinetics, pharmacodynamics, and adverse effects of digoxin and levosimendan (Sept 2013)

	Digoxin	**Levosimendan**
Description/indication	Digoxin is a cardiac glycoside derived from the digitalis (foxglove) plant. It is used in the management of cardiac arrhythmias and cardiac failure.	Levosimendan is a relatively new inodilator agent used in the short-term management of severe cardiac failure.
Pharmaceutical aspects	PO formulation 6.25mcg/250mcg tablets or in IV formula in varying strengths. Has a narrow therapeutic window (1-2mcg/L) and a wide side effect profile requiring frequent monitoring	Presented in an IV form only, 2.5mg/ml
Pharmacodynamics	Direct action is via inhibition of Na/K ATPase resulting in increased intracellular Na concentrations, which 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 better LV output.	Levosimendan sensitizes cardiac myocytes to calcium by binding to cardiac troponin C. It also binds to K ATP channels in vascular smooth muscle to cause vasodilatation. Hence it reduces preload and afterload and improves myocardial blood supply. At higher doses it appears to have an inhibitory effects on PDE3 (increasing cellular CAMP levels and thus intracellular calcium to increase contractility).
Side effects	CVS - arrhythmias, conduction block (prolonged QRS/PR/QT) GIT - anorexia, N/V, weight loss CNS - malaise, fatigue, headache, visual changes, confusion These may be exacerbated by electrolyte abnormalities	Alterations in K channel function theoretically give an increased risk of arrhythmias. May cause hypotension due to vasodilatation. Use caution in patients with renal or hepatic impairment.
Pharmacokinetics		
Administration	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 it to an inactive metabolite) Time to onset - 1-2 hours PO, minutes IV	Route - IV only Dose - loading dose 6-24mcg/kg over 10 min then continuous infusion 0.05-0.2mcg/kg/min Bioavailability - 100%
Distribution	Volume of distribution 5-11L/kg. Principle reservoir skeletal muscle (hence dosing should be based on lean muscle mass) Protein binding 25%	Protein binding - high >90% Peak concentration reached after 48 hrs
Metabolism	Sugar sequences hydrolysed in gut, removal of lactone ring by gut bacteria, most of drug excreted unchanged	Complete metabolism to inactive metabolites
Elimination	Mostly in urine unchanged, half life 36-48 hrs	Half-life of parent drug 1 hr, active metabolites 70 hours, excreted in urine (hence dose reduce in renal failure). Cardiac effects continue for 2-7 days post 24 hour infusion