Q8 Compare and contrast adrenaline and levosimendan (March 2012)

	Adrenaline	**Levosimendan**
Description/indication	Adrenaline is an endogenous catecholamine released from the mammalian postganglionic sympathetic nerve terminals. It also makes up 80% of the catecholamine contents of the adrenal medulla. It is used in the setting of unstable cardiovascular parameters, as part of the ALS protocol for cardiac arrest, in anaphylaxis as a mast cell stabiliser, for severe asthma and in local anaesthetic solutions to cause local vasoconstriction.	Levosimendan is a relatively new inodilator agent used in the short-term management of severe cardiac failure.
Pharmaceutical aspects	Synthetic adrenaline is presented as a clear solution of varying strengths - 1:1000, which contains 1mg/ml (usually 5 or 10ml vials) and 1:10000, which contains 1mg/10ml. It can also be nebulised.	Presented in an IV form only, 2.5mg/ml
Pharmacodynamics	Adrenaline typically exerts is effects through beta agonism at low doses (increasing inotropy and chronotropy) and causing smooth muscle relaxation (including bronchial SM and vasodilatation). At higher doses it displays alpha effects and causes vasoconstriction. It also stabilises mast cells to prevent degranulation.	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)
Pharmacokinetics		
- Administration	Route - IV, IM, S/C, NEB, ETT Dose - 1mg ALS, 0.1mg anaphylaxis, titrated dose for haemodynamic instability (commence at 0.01mcg/kg/min, increase for alpha effects) Bioavailability - 100% Onset to action - seconds	Route - IV only Dose - loading dose 6-24mcg/kg over 10 min then continuous infusion 0.05-0.2mcg/kg/min Bioavailability - 100%
- Distribution	Does not cross the BBB 50% protein bound	Protein binding - high >90% Peak concentration reached after 48 hrs
- Metabolism	Taken up by the sympathetic nerve terminals and metabolised via COMT and MAO, circulating Adr metabolised via COMT	Complete hepatic metabolism to active metabolites
- Elimination	90% excreted via urine as inactive metabolites Half life 2 min, longer for infusion (5-10min)	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
Side effects	Larger side effect profile than Nad as in addition to potentially causing HTN, tachycardia and arrhythmias, has metabolic SE (glycogenolysis, lipolysis, gluconeogenesis) and can increase BMR. Can worsen PHTN (causes pulm vasoconstriction). Should be administered via central line except in arrest situations as can cause necrosis if extravasates.	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.