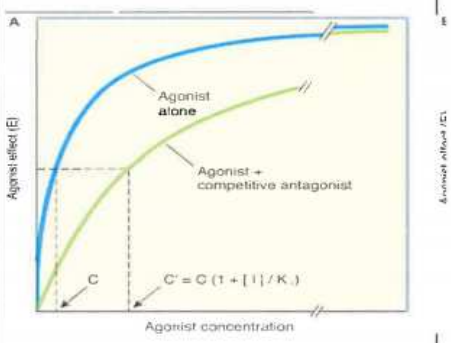
2014.2D

Question 1 Biotransformation – Phase 1 and 2 reactions with an emphasis on Suxamethonium (Chp 4) **Subject:** Pharm LOA: 1	What is drug biotransformation?	Drug metabolism to allow drugs to become **inactive or by increasing excretion** by making them more hydrophilic, or by metabolising them to less active agent.	Bold
	Describe phase 1 and phase 2 reactions?	Phase 1 – **unmasking functional group** (-OH, -NH2, -SH) to become more polar metabolite. Includes oxidation, deamination, hydrolysis, reductions Phase 2- **conjugation with endogenous substrate** to become highly polar conjugate	Bold
	How is Suxamethonium metabolised? Why may a patient have a prolonged paralysis following Sux	**Rapid phase 1 hydrolysis** by **butyrycholinesterase and pseudocholinesterase** in liver and plasma Genetically deficient in BCHE so slowed metabolism	One of the bold

2014.1D

Question 1 Clearance Definition, factors affecting, examples **Subject:** Pharmacology LOA: 1	(a) What is drug clearance?	(a) **Clearance:** • Measure of the ability of the body to eliminate a drug • Rate of elimination in relation to drug concentration • CL = rate of elimination / concentration	(a) Reasonable definition to pass
	(b) What factors affect drug clearance?	• Concentration - **Dose & Bioavailability** • Elimination - **specific organ function / blood flow & protein binding** • Major sites of elimination are kidneys and liver – therefore factors that affect these organs' function and blood flow will have most effect	(b) One for each element
	(c) What is the difference between capacity-limited and flow-dependent drug elimination?	(c) **Capacity-limited is saturable (zero order)** Examples: aspirin, phenytoin, ethanol. **Flow-dependent = non-saturable (1st order)** (organ blood flow, protein binding) Examples: Alprenolol / amitriptyline / Imipramine / isoniazid / labetalol / lignocaine / Morphine / propoxyphene / propranonol / verapamil	(c) Bold to pass

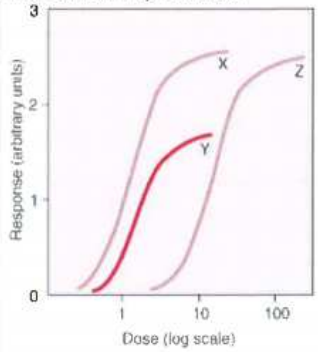
2013.2D

PHARMACOLOGY Question 1 LOA: 1	1. What is an antagonist?	1. Receptor antagonists **bind to receptors** but do **not activate** them. The primary action of antagonists is to **prevent agonists from activating receptors.**	Bold to pass
	2. What is the difference between a competitive and non-competitive antagonist?	2. Competitive antagonist: In the presence of **increasing concentration of antagonist, higher concentrations of agonist will produce a given effect.** Eg propanolol and noradrenaline / adrenaline. Irreversible or non competitive antagonist Bind via covalent bonds or **just binding so tightly to receptor so receptor unavailable** for agonist. Duration of action of antagonist depend on rate of turnover of receptor-antagonist molecules.	
	What type of antagonist is naloxone?	Competitive	
	3. What effect does a competitive antagonist have on the concentration-effect curve?	3. Shift agonist vs effect **curve to right. Higher concentrations of agonist can overcome competitive antagonist** 	

2013.2D

PHARMACOLOGY Question 1 LOA: 1	1. Define drug elimination half life Prompt: Is there a formula you can use?	**Time required to change the amount of drug in the body by ½ during elimination** T1/2 = 0.7 x Vd/clearance (0.7 approx log 2) 50% after 1, >90% after 4	Bold to pass
	2. How does knowledge of a drug's half life help us clinically?	Dosing regimens Decay afterdose/overdose Time to steady state after dose change	2 to pass
	3. What disease states cab affect elimination half-life?	Liver, renal, cardiac disease	one organ
	4. What disease state could affect the elimination half-life of morphine?	Liver, renal	one organ

2013.1.2

Question 1: **POTENCY & EFFICACY** LOA: 1	Define "potency".	Potency refers to the affinity or attraction between an agonist and its receptor. It reflects the dose axis of dose response curves. A measure of drug potency is the EC_{50} – the conc'n/dose req'd to produce 50% of maximal response.	**Be able to explain potency and efficacy**
	How is this different to Efficacy?	Efficacy is the maximal response that a drug (agonist) can produce (E_{max}) when all receptors are occupied, irrespective of the concentration required to produce that response. Efficacy determines a drugs clinical effectiveness and reflects the response axis	
	Draw a concentration-response curve showing 2 drugs with the same potency but different efficacy.	 X and Z have similar efficacies, X and Y have similar potencies; X and Y are more potent than Z	

2013.1.3

Question 1: Bioavailability LOA: 2	What is bioavailability?	Fraction of **unchanged drug** reaching the **systemic circulation** following administration by any route.	**Bold to pass**
	What factors limit drug bioavailability following oral administration?	**Extent of absorption:** **a) Property of the drug** eg hydrophyllic vs lipophyllic b) Gut factors - reverse transporter pumps p-glycoprotein &gut wall metabolism **First pass elimination-** metabolism by liver before reaching systemic circulation or small effect biliary excretion	**Bold to pass**
	How can you overcome the effects of high first pass metabolism?	**Change route of administration** to sublingual, transdermal eg GTN, rectal, inhalation, IV, IM **Increase dose** Use pro-drugs	**Bold**

2012.1.1

Question 1 LOA: 1 **HALF LIFE**	Define drug elimination half life	**Time required to change the amount of drug in the body by ½ during elimination**	Concept required
	Is there a formula you can use? *Prompt: What factors affect half-life?* *Prompt: Can you explain what that means?*	T1/2 = 0.7 x Vd/clearance (0.7 approx log 2)	Both bold to pass
	How does knowledge of a drug's half life help us clinically?	**Indicates time to steady state after dose change.** 50% after 1, >90% after 4	

2012.1.2

Question 1 LOA: 1 **PARTIAL AGONIST**	In the context of drug-receptor interactions, what is the difference between a full agonist and a partial agonist? Under what circumstances can a partial agonist act as a antagonist? *Prompt: Can you use opioids as an example?*	**High concentrations of full agonists can evoke a maximal response, but partial agonists cannot evoke maximal response at any concentration** In the presence of a full agonist Buprenorphine	

2012.1.3

Question 1: LOA: 1 **DIFFERENCES IN DRUG METABOLISM**	What factors determine the difference in drug metabolism between individuals?	**Genetic** – enzyme level differences Diet – induce / inhibit enzymes Environmental – exposure to enzyme inducers **Age** – extremes have decreased enzyme activity or decreased levels of cofactors Sex – increased metabolic rate in males **Drug-drug interactions** – enzyme induction or inhibition, substrate competition **Disease states** - hepatic, pulmonary, cardiac, thyroid, inflammatory Liver size & function Circadian rhythm Body temperature	3 of 4 **bold** to pass
	What is meant by "enzyme induction"? *Prompt: What effect does it have on metabolism?* *Prompt: What effect does this have on the pharmacological action of the drug?*	Drug causes an increased rate of synthesis or decreased rate of degradation of enzyme causing: **accelerated substrate metabolism** **decreased pharmacological action** of the inducer or a co-administered drug.	**Bold** to pass

2012.2.1

Question 1 Clearance-renal and hepatic	What is drug clearance?	Clearance predicts the rate of elimination in relation to drug concentration. **CL=rate of elimination/concentration**	**Bold**
LOA 1	Which organs are involved in drug clearance?	2 main organs are **kidney and liver**, others are blood, muscle, lung. CL systemic= CL liver + CL kidney + CL other	**Bold**
	What factors affect renal clearance?	**Renal function, renal blood flow**, plasma protein binding, ionization	Bold
	Please name drugs that are predominantly cleared by the kidneys?	ampicillin, **gentamicin**, vancomicin, digoxin, enalapril, metformin, lithium	At least bold plus 2 others-prompt: Any drugs that need dose changes in patients with poor renal function?

2012.2.2

Question 1 Volume of distribution LOA: 1	Define the "volume of distribution" of a drug.	Defined as the volume in which the amount of drug in the body would need to be uniformly distributed to produce the observed concentration in blood, plasma or water. Vd = Amt drug in body/C	Pass: either definition or formula
	How is it possible for a drug to have a VD of 2500L in an adult?	**Higher concentrations in extra vascular tissues than in blood – e.g. lipid soluble** (not homogeneously distributed)	Pass: either not homogeneously distributed or extra vascular tissue higher conc
	Give an example of a drug with a: - high VD - low VD	High: Morphine, chloroquine, digoxin, clonidine, fluoexitine, tricyclics, β blockers, diazepam, Low/approximating ECF/TBW: aspirin, frusemide, antibiotics (gentamicin, amoxicillin, cephalexin), tolbutamide, phenytoin, valproic acid, lithium, warfarin, theophylline, indomethacin, sulphamethoxazole.	**One of each** **One of each**
	What is the importance of Vd in the overdose situation PROMPT – for example (drug name)?	**Drugs with large Vd (TCAs) cannot be dialyzed** whereas **drugs with a low Vd (ASA, lithium)** can.	**Bold**– use these to prompt; should be able to designate "high" or "low" VD to pass.

2012.2.3

Question 1 Signalling mechanisms LOA: 1	List the various molecular mechanisms of transmembrane signalling.	1. Lipid soluble ligand crosses membrane and binds to intracellular receptor. 2. Transmembrane receptor protein with ligand binding to extracellular domain regulating intracellular enzymatic activity 3. Transmembrane receptor protein that binds and stimulates protein tyrosine kinase 4. Ligand-gated transmembrane ion channels 5. Transmembrane receptor protein, G protein, intracellular second messenger	Describe 3 mechanisms to pass
	Describe the function of the system involving G proteins	Transmembrane signally system with 3 separate components. Extracellular ligand binds to specific **cell surface receptor**. This receptor then activates **G protein** located on cytoplasmic surface of membrane. Activated G protein changes activity of **effector element** (enzyme or ion channel) leading to a change in concentration of **second messenger**.	Bold concepts to pass
	Give an example of a drug that acts via this system.	B agonist: B adrenoreceptor, G_s protein, adenylcyclase, increased concentration cAMP. (other examples include glucagon, thyrotropin, histamine, serotonin, acetylcholine, opioids)	Correct example to pass. Extra points for describing components

2011.1.1

Variables of Drug Absorption	What variables influence the extent & rate which a drug is absorbed?	1.**Route of administration- PO; SC; SL; PR** **2. Nature of the absorbing surface** **(a) Cell membrane –** single layer of intestinal epi cells compare to several layers of skin cells. **(b) Surface area –** lung, small intestine, stomach **3.Blood Flow –**blood flow enhances absorption SL v SC **4. Drug Solubility –** lipid soluble drugs **-** **5. Drug Formulation –** i.e. enteric coatings	Need 3 of main concepts
	Explain why aspirin absorption is enhanced by the low pH in the stomach?	Aspirin is an **acidic drug** (pKa 2.98) relatively **un-ionised in the stomach** & more ionised in the small intestine (i.e. absorbed more readily from stomach)	Aspirin is more lipid soluble in stomach & absorption is greater here
	Prompt: How does ionisation of a drug affect it's solubility?	Drugs exist as **weak acids or weak bases** & in the body they are either **ionised or un-ionised; Ionised**(charged polar) **water soluble; Un-ionised** (non-polar) **lipid soluble**	Need to correctly state un-ionised drugs lipid soluble

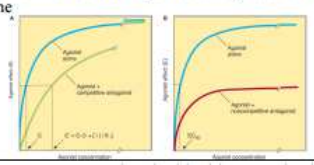
2011.1.2

Drug metabolism	Describe Phase 1 and Phase 2 reactions in drug metabolism. Prompt 1: What are some of the biochemical reactions that characterize phase 1 reactions? (Oxidation, reduction, hydrolysis) Prompt 2: How does phase 2 reactions enhance the excretion of a drug?	Process of **chemical modification of a drug leading to more hydrophilic, more polar, readily excreted compound.** Phase 1 (Functionalization) reactions: converts parent drug to **more polar often inactive metabolite –** process of oxidation, reduction, hydrolysis where polar functional group (OH, N H2,SH) is introduced**-** majority reaction via cytochrome P450 enzymes. Phase 2 (**Conjugation**) reactions: metabolites combine with endogenous glucuronic a, sulphate, acetylcoenzyme A or glutathione to **form more polar metabolite-** reactions catalysed by different transferase enzymes. Note: Phase 1&2 can occur alone, sequentially or simultaneously. Metabolites can be more active or toxic than the parent drugs.	Pass: Need basic understanding of in general "metabolise to more polar and excretable compounds" **Phase 1** 1 example: (oxidation, reduction, hydrolysis) CYP450 **Phase 2** 1 example: Conjugation to form more polar compound+ one example of the endogenous substances

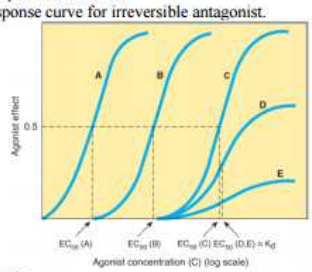
2011.1.3

Volume of Distribution	Define the "volume of distribution" of a drug.	**Defined as the volume in which the amount of drug in the body would need to be uniformly distributed to produce the observed concentration in the blood.** Vd = **Total amount of drug in body/conc in plasma or blood**	Pass: either definition or formula
	What factors affect volume of distribution? (prompt: consider drug/patient factors)	**Drug properties –** lipid solubility; pKa; pH; protein binding; **Patient factors –** age; gender; disease state; body composition (fat distribution); blood flow	Pass: 2 factors from each
	Give example of drugs with high and low Vd.	High Vd: diazepam; β blockers; tricyclics; digoxin; morphine; clonidine; fluoxetine; chloroquine; cyclosporin Low Vd: warfarin; lithium; phenytoin; aspirin; frusemide; valproic acid; tolbutamide; cephalexin	Pass: two from each group

2011.2.1

Question 1 Competitive and non-competitive antagonists	a) What is an antagonist? b) What is the difference between a competitive and non-competitive antagonist?	a) Receptor antagonists bind to receptors but **do not activate** them. The primary action of antagonists is to prevent agonists from activating receptors. b)Competitive antagonist In the presence of increasing concentration of antagonist, **higher concentrations of agonist will produce a given effect**. Eg propanolol and noradrenaline / adrenaline Shift agonist vs effect curve to right. **Higher concentrations of agonist can overcome competitive antagonist** Irreversible or non competitive antagonist Bind via covalent bonds or just binding so tightly to receptor **so receptor unavailable for agonist**. Duration of action of antagonist depend on rate of turnover of receptor-antagonist molecules. **Reduces maximal effect of agonist** but may not affect its EC50. eg phenoxybenzamine vs adrenaline 	Must have good understanding of what happens with increasing agonist doses in both cases.

2011.2.2

Question 1 Drug concentration and response	a) In relation to drug concentration and responses, what is the EC50? b) What are spare receptors?	a) EC50 is the **concentration at which an agonist produces half its maximal effect**. **b) Need to understand concept of spare receptors.** The concentration of agonist producing a maximum response may not result in occupancy of full complement of receptors. These receptors are said to be "spare." Temporal or in number Dose-response curve for irreversible antagonist.  A = no antagonist B = low dose antagonist. Still get maximum effect because receptors still in excess of required for effect C = Largest concentration of antagonist to produce maximum effect. Therefore no spare receptors. D + E = high concentrations of antagonist which diminish maximum response	Good understanding of bolded

2011.2.3

Question 1 Bioavailability	a) Define bioavailability b) What factors affect bioavailability c) How can you overcome the effects of high first pass metabolism?	**a) Fraction of unchanged drug reaching systemic circulation following administration by any route.** AUC (conc-time) is a common measure of the extent of bioavailability. b) 3 Factors **a) Extent of Absorption** i) Too Hydrophilic or too lipophilic ii) Reverse transporter associated with P-glycoprotein – pumps drug back to gut lumen iii) Gut wall metabolism **b) First Pass Elimination** i) Metabolism by liver before it reaches systemic circulation ii) Small additional affect if drug has biliary excretion c) Rate of Absorption i) Determined by site of administration and drug formulation c) **Change route of admin to**: Sublingual, transdermal, rectal, inhalation, IV, IM ; increase dose	Bolded Bolded **(Need 2 routes of admin)**

2010.1.1

Question 1: Spare receptors & their significance P13-4	1. Define the term "spare receptor" 2. What is the significance of spare receptors? *How is it related to the maximal response of a drug?* *What do the terms spare in number and temporal spareness mean?*	**Receptors "spare" if maximal biologic response possible at an agonist concentration that does not result in all available receptors being occupied.** Describes concept of receptors "spare in number". Can also have spareness "temporally" if effects produced by binding last much longer than the time the agonist occupied the receptor Increasing the number of receptors coupled to an effector can allow lower concentrations of agonist to still produce a given proportion of maximal response - tissue thus more sensitive	Highlighted section concept concept

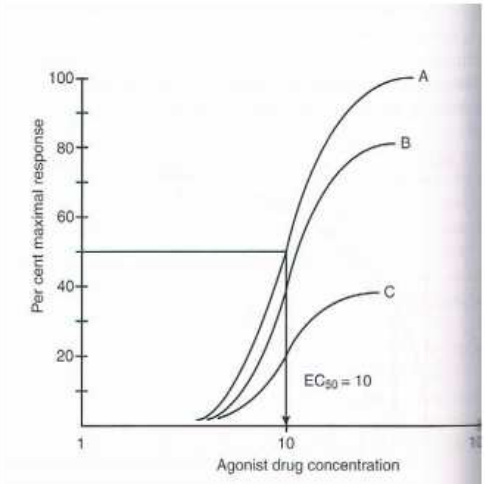
2010.1.2

Question 1: Antagonist / agonists P14-16	1. Describe the difference between a Competitive and an Irreversible antagonist	Competitive - in fixed conc. of agonist, increasing conc. of antagonist will lead to progressively inhibited response, but an increasing agonist conc. can overcome to still evoke maximal response (agonist conc / effect curve shift to right) High comp. antagonist conc. prevent response completely if agonist conc. fixed Irreversible (Noncompetitive) - bind so tightly or covalently as to make receptor unavailable to agonist. Number of remaining receptors may then be too low to allow maximal response to occur regardless of agonist conc. (unless spare receptors) Length of effect of irrev. antagonist will reflect turnover of receptors involved rather than rate of elimination of antagonist	Description visual or verbal
	2. Give an example of an antagonist?	Competitive: naloxone, flumazenil, Propranolol, isoprenaline, naltrexone, nalmefene Irreversible: phenoxyenzamine, MAOI	1 example

2010.1.3

Question 1: Second messengers P21-26	1. What are the steps in activation of a second messenger?	Method of transmembrane signalling Drug binds to a receptor on extracellular side plasma membrane Triggers activation of G protein on cytoplasmic side Activated G protein changes an enzyme or ion channel This changes concentration of intracellular second messenger which mediates a response	Binding Transmembrane signal G protein Effector
	2. Give an example of a second messenger and the type of response it produces? *What about cAMP?*	cAMP via adenylate cyclase Mobilization of fat and carbohydrates Conservation of water by kidney Increase rate and contractility of heart Ca++ regulation Adrenal hormone regulation, relaxation of smooth muscle Ca++ and Phosphoinositides cGMP via transmembrane guanylyl cyclase (atrial naturetic peptide) or nitric oxide which binds to a cytoplasmic guanylyl cyclase GTN, Na nitroprusside Inhibition of phosphodiesterase – increased cGMP eg sildenafil	name 1 and some knowledge of a response

2010.2.1

1. a. With regard to drugs, what is "potency".	Potency refers to the affinity or attraction between an agonist and its receptor. A good measure of drug potency is the EC_{50} – the concentration that produces 50% of the maximal response.	Demonstrate understanding of efficacy and potency.
b. How is this different to Efficacy?	Efficacy is the maximal response that a drug (agonist) can produce (E_{max}) when all receptors are occupied, irrespective of the concentration required to produce that response.	
c. Draw a concentration-response curve showing 2 drugs with the same potency but different efficacy.		

2010.2.2

1. a. What routes of drug administration are there?	Enteral: Sublingual, buccal, oral, rectal Parenteral: SC, IM, IV, intrathecal, epidural Inhalational Topical	**Enteral/oral** + 3 non-enteral
b. What factors affect the rate of drug absorption from the small intestine?	Ionisation status of drug: alkaline Intestinal pH (7-8) favours absorption of un-ionised basic drugs Intestinal motility; increased motility lead to reduced transit time and drug absorption Gut surface area, blood flow, solubility of drug, formulation of drug **PROMPT: What is a specific drug factor**	Must mention drug factors and gut factors
c. What are potential disadvantages of rectal drug administration?	Erratic absorption because of rectal contents Local drug irritation Uncertainty of drug retention	1/3

2010.2.3

1. a. What is meant by Total Body Clearance" of a drug	Describes the **ability of the body to eliminate a drug**. It refers to the theoretical volume of plasma emptied of drug per unit time (usually L/h). Total body clearance reflects the sum of all clearance process including **renal**, **hepatic** and **other**.	Definition
b. Name 2 drugs that have a high hepatic clearance and explain why this is important.	Lignocaine, Morphine, Propranolol, Pethidine. Drugs with high hepatic elimination may only be suitable for parenteral administration or have significant dosing variations depending on the route of administration. **PROMPT: How might it impact on route of administration**	2 drugs Demonstrate understanding
c. What factors determine drug half-life	Volume of Distribution and Clearance ($t_{1/2}$ = 0.693 x Vd/ Cl) Vd and clearance change with disease states - cardiac, hepatic and renal failure	Vd and clearance

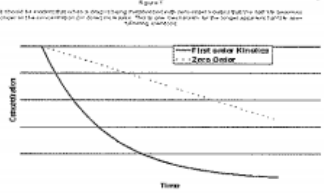
2009.1.1

Question 1: Volume of Distribution	1. Define the "Volume of Distribution" of a drug	The apparent volume that a drug would occupy if it was evenly distributed according to its measured concentration in blood, plasma or water. Vd = Amount of drug in body / Concentration in plasma or blood	Pass: either definition or formula
	2. Fluoxetine has a volume of distribution of 2500L/70kg. What does this mean?	Has higher concentration in extravascular tissues than in the vascular compartment. high lipid solubility	
	3. Give an example of a drug with a low volume of distribution	aspirin, NSAIDS, warfarin, most antibiotics, tolbutamide	

2009.1.2

Question 1: Drug Half-life	1. What is the definition of drug half-life?	1. time to change amount of drug in body by one half during elim (or infusion) OR t1/2 = (0.7 x Vd)/clearance	Either definition or formula
	2. What disease states can affect drug half life?	2. Factors affecting Vd: malnutrition, albumin levels, change in muscle mass or fat distribution, oedema, ascites, effusions Factors affecting CL: poor nutrition, renal disease, hepatic disease, heart disease(CO)	Need 2 Vd factors, and renal plus one other for CL

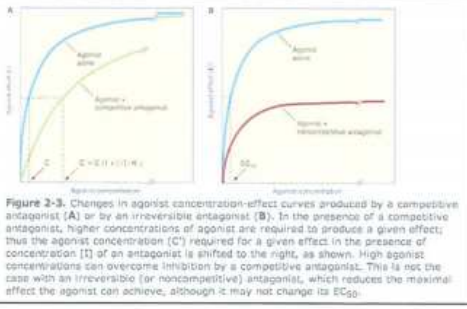
2009.1.3

Question 1. Zero and First order kinetics	1. What is "First order elimination kinetics"?	First order: A constant fraction/percentage of the drug is eliminated per unit time. Rate of elimination is proportional to the amount of drug in the body. t½ constant. Most drugs eliminated this way (____) 	Definition to pass
	2. How is it different to zero order kinetics? (prompt – capacity-limited)	Zero order: a constant amount of drug is eliminated per unit time. Rate of elimination is constant and is independent of drug. There is capacity limited clearance or mechanisms have been saturated in overdose.	
	3. Give some examples of drugs with zero order kinetics?	Examples: Ethanol, phenytoin, salicylates, theophylline, and thiopentone (at high doses) (.....)	2 examples to pass

2009.2.1

Question 1: **Drug Biotransformation**	(a) What are the sites of drug biotransformation? (Prompt – Which is the major?)	**Liver** - GIT - lung - skin - kidneys	Must get Liver and two others
	(b) What is a **Phase 1 biotransformation** reaction?	Conversion of a parent drug to a **more polar / water soluble** form by the adding or unmasking of a **functional group**, most commonly by **oxidation** but also by reduction or hydrolysis. The hepatic CYP (P450) enzymes are responsible for the majority of these reactions.	Must mention **more polar** or **water soluble** & **oxidation**
	(c) What is meant by **enzyme induction,** in liver biotransformation?	**Repeated administration** of a substrate brings about either **enhanced enzyme synthesis** or **reduced enzyme degradation** causing **increased metabolism** of the substrate	Must mention **enzyme more active**, therefore **increased metabolism and reduced drug action** (2 of 3 bolds to pass)

2009.2.2

Question 1: **Dose Response**	(a) Draw and explain a Dose-Response curve for an agonist		Must demonstrate relationship of concentration to effect
	(b) Show how this curve is altered in the presence of an irreversible (non-competitive) antagonist	 Figure 2-3. Changes in agonist concentration-effect curves produced by a competitive antagonist (A) or by an irreversible antagonist (B). In the presence of a competitive antagonist, higher concentrations of agonist are required to produce a given effect; thus the agonist concentration ([C']) required for a given effect in the presence of concentration [I] of an antagonist is shifted to the right, as shown. High agonist concentrations can overcome inhibition by a competitive antagonist. This is not the case with an irreversible (or noncompetitive) antagonist, which reduces the maximal effect the agonist can achieve, although it may not change its EC_{50}.	Pass - Non-competitive antagonist has lower maximal effect
	(c) How does this differ from a competitive antagonist?		Pass – Higher conc. of agonist to produce similar effect

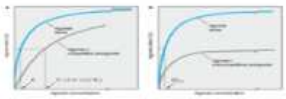
2009.2.3

Question 1: **Drug Clearance**	(a) What formula describes **Drug Clearance**?	Ratio of rate of elimination of a drug to its concentration in blood / plasma or $CL = \frac{\text{Rate of elimination}}{\text{Conc}}$	Must get formula to pass
	(b) What is **Flow Dependent Elimination**? (prompt if needed – High extraction)	For drugs that are readily cleared by their organ of elimination (high extraction ratio), **the rate of elimination is dependent on rate of drug delivery to the organ – determined by blood flow** and plasma protein binding. (Systemic CL = CL_{renal} + CL_{liver} + CL_{other})	Must mention **drug delivery / blood flow** to pass.
	(c) Can you name any drugs that have Flow dependent elimination	Hepatic –lignocaine; propanolol; verapamil' morphine; pethidine	One example to pass

2008.1.1

Second Messengers	In reference to drug action what is a second messenger? What steps are involved in the action of a drug via a second messenger ? (Prompt - Illustrate this with an example)	A chemical eg Ca++ or cAMP that converts receptor binding to end effect through the production of an active intracellular element. Extracellular ligand specifically detected by a cell-surface receptor. Receptor triggers the activation of a G protein located on the cytoplasmic face of the plasma membrane. Activated G protein changes the activity of an effector element (usually enzyme or ion channel) This element changes the concentration of the intracellular second messenger. Example cAMP - Gs stimulates adenylyl cyclase which converts intracellular ATP to cAMP which stimulates cAMP-dependent protein kinases. Ca, Phosphoinositides cGMP (Pass –understanding of the concept that there may be a secondary process producing drug effect and able to name at least 1 second messenger)	

2008.1.2

Competitive vs Irreversible Antagonists	What is an antagonist ? Explain the difference between a competitive and irreversible antagonist (Illustrate this with an example)	Receptor antagonists bind to receptors but do not activate them. The primary action of antagonists is to prevent agonists from activating receptors In the presence of a fixed concentration of agonist, increasing concentrations of a reversible **competitive antagonist** progressively inhibit the agonist response; high antagonist concentrations prevent response completely. eg Propranolol and Noradrenaline **Irreversible** antagonists bind to the receptor either by forming a covalent bond with the receptor or by binding so tightly that the receptor is unavailable for binding of the agonist eg Phenoxybenzamine vs adrenaline  Changes in agonist concentration-effect curves produced by a competitive antagonist (Panel **A**) or by an irreversible antagonist (Panel **B**). In the presence of a competitive antagonist, higher concentrations of agonist are required to produce a given effect; thus the agonist concentration (C') required for a given effect in the presence of concentration [I] of an antagonist is shifted to the right, as shown. High agonist concentrations can overcome inhibition by a competitive antagonist. This is not the case with an irreversible (or noncompetitive) antagonist, which reduces the maximal effect the agonist can achieve, although it may not change its EC_{50}. Pass Be able to distinguish between competitive and irreversible antagonist	

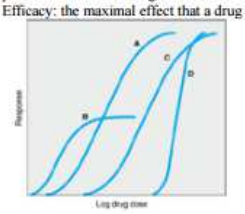
2008.1.3

Bioavailability	Define the term bioavailability What factors limit drug bioavailability following oral administration ? What methods of drug delivery are used to overcome bioavailability problems ?	Fraction of unchanged drug reaching the systemic circulation following administration by any route. (1) Extent of absorption (2) First-pass elimination (liver, gut) Alternative route – sublingual, rectal, transdermal parenteral Administration pro-drug, increased dose	Need close approximation of defn Identify both factors (prompt if necessary) Give one example of an alternative route

2008.2.1

Question 1: First Pass effect	1. What is first pass effect? Prompt "Can you define first pass effect?" 2. How can the first pass effect be reduced?	After absorption of an orally ingested drug, portal blood delivers drug to liver. •Metabolised in gut wall. •Metabolised in portal blood. •Metabolised by liver. •Excreted into bile Fraction of unchanged drug reaching systemic circulation may be reduced. ie. Reduces bio-availability of a drug Different route of administration IV; IM/SC; Sublingual; Transdermal; PR – Still may have some first pass metabolism, only 50% bypasses liver; Inhalational (may have first pass effect in the lung). Intrathecal	Pass: basic definition Mention 4 alternative routes

2008.2.2

Question 1: Efficacy and Potency	1. What is the difference between Efficacy and Potency? Prompt: You can draw a diagram if you like?	Potency: the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of that drug's maximal effect. Efficacy: the maximal effect that a drug exerts.  	Definitions to pass **Examiner note: Drugs A and B are more potent than drugs C and D** because of the relative positions of their dose-response curves along the dose axis. **Drugs A, C, and D have equal maximal efficacy**, while all have greater maximal efficacy than drug B.
	2. What factors affect a drug's efficacy?	Affinity of receptor for drug; the drug-receptor interaction. . The route of administration, absorption, distribution through the body, and clearance from the blood or site of action	3 out of 6 to pass (NB not to do with potency)

2008.2.3

Question 1: P450 enzyme system	1. What is the role of the cytochrome P450 enzyme system? *Prompt: what does CP450 do?*	**Part of biotransformation system to detoxify drugs/substrates** **Acts by oxidation (phase 1 reaction)**: one molecule of oxygen is consumed per molecule of substrate Makes substrates more polar – easier to excrete or conjugate (phase2). Located on smooth endoplasmic reticulum Acts on a large number of lipophilic substrates, low specificity Relies on two enzymes: cytochrome P450, CP450 reductase (plus oxygen, NAPDH). **CP450 is a hemo-protein** – active in the oxidized -ferric state-Fe3+	Bold to pass
	2. What is the mechanism of CP450 enzyme induction and give examples?	Enhanced rate of synthesis - Reduced rate of degradation of CP450 enzyme Specific enzyme inducers eg: CYP/CP 450 2B1 - **barbiturates** CP 450 3A –steroids, macrolides, **anticonvulsants** CP 450 2E1 – isoniazid, chronic **ethanol** CP 450 1A1 – pollutants – aromatic hydrocarbons in tobacco smoke	1 mechanism and 2 examples

Older

FIRST QUESTION	What do you understand by volume of distribution	
	Volume of distribution is the measure of the apparent space in the body available to contain the drug **It relates the amount of drug in the body to the concentration of the drug in blood or plasma** **Vd = Amt drug in body/C** Drugs with a high volume of distribution are very tightly bound by tissues compared with blood, so have a much higher concentration in extravascular tissue than in the vascular compartment. If the drug is tightly bound to plasma proteins and not tissues it has a small volume of distribution	
SECOND QUESTION	What factors affect volume of distribution	
	Drug properties – lipid solubility, pKa, pH, protein binding, blood flow Patient properties – age, gender, disease, body composition	2 each 2 each
THIRD QUESTION	What is the importance of Vd in the overdose situation PROMPT – for example?	
	Drugs with large Vd (TCAs) cannot be dialyzed whereas drugs with a small Vd (ASA, lithium) can	1

FIRST QUESTION	What do you understand by biotransformation	
	Metabolism transforms lipophilic to more polar, more excretable products Phase I reaction – converts parent drug to more polar often inactive metabolite – process of oxidation, reduction, hydrolysis where functional group (OH,N H2,SH) is introduced or unmasked – polar metabolites are readily excreted Less polar metabolites combine with glucuronic a, sulfuric a, acetic a or amino a to form polar metabolite = conjugation = Phase II reaction	
SECOND QUESTION	Where does biotransformation occur?	
	Between absorption and renal elimination **Liver principal organ** **Intestine** – clonazepam, chlorpromazine Gastric acid – penicillin Digestive enzymes – insulin Enzymes in wall of intestine – sympathy.catecholam.	Liver + one other

Second messenger	What do you understand by the term second messenger ? Please describe the common steps in the mechanism of their activation (Explain the concept of spare receptors ?)	Reasonable example/understanding Ligand/receptor binding G protein Effector element changes second messenger concentration Bonus question	

Evaluation of new drugs	Describe the phases of testing of a new drug Please describe ways in which new drugs might be discovered or produced	In vitro/animal, human phases 1-4 2 of chemical modification, random screening, rational design, gene methods, new drug target identification	

Pharmacokinetics in the elderly	Outline the changes in pharmacokinetics that occur in the elderly How does the pharmacokinetics of gentamycin change in the elderly ?	Cover 2 of 4 with description - absorption, distribution, metabolism, excretion Decreased renal excretion increases half life	

Second messengers pp 21-5	1. What do you understand by the term 'second messenger'?	A second messenger is an intracellular substance which has its concentration altered by a process initiated by an extracellular ligand. The second messenger then acts to initiate or facilitate an intracellular process. 3 basic steps 1.Extracellular process [EC] 2.Transmembrane signalling system [TM] 3.Intracellular process[IC]	Must give reasonable explanation / example	
	2. Describe the **common** steps in the activation of second messengers?	Extracellular **ligand** [EC] Cell surface **receptor** activated via ligand detection[EC] **G protein** activation [TM] Concentration change of an **effector** element [enzyme or ion channel][TM] Change in **second messenger** concentration[IC] Second messenger action on a **substrate or enzyme**[IC] **Response**[IC]	To pass: Must indicate 2/3 basic steps and have a reasonable idea of the details of each step either generically or by example	
	3.Can you give examples of second messengers?	1.Cyclic AMP 2.Calcium and phosphoinositides 3.Cyclic GMP	To pass:[At least 2/3 required]	

Antagonist/ Agonist/ Partial agonist	1. How does an irreversible antagonist alter the concentration effect curve for a drug? (Draw the curve to demonstrate.) (What happens to EC50?)	**Draws curve for agonist alone. Draws curve for agonist plus irreversible antagonist. Reduced maximum effect.** EC50 may not alter.	Ask about maximum effect and EC50.	
	2. How does this compare to a competitive antagonist? (Draw the curve to demonstrate.)	**Draws curve shifted to right, with EC50 increased and maximum effect not changed.**	Ask about maximum effect and EC 50.	
	3. Which of these does the curve for a partial agonist most resemble?	Irreversible antagonist.	**Bold items required to pass.**	

Bio-availability	1. Define bioavailability.	The fraction of unchanged drug reaching the systemic circulation following administration by any route.	All!	
	2. What are the reasons why an orally administered drug might have less than 100% bioavailability?	Imperfect absorption First pass effect Degradation by bugs in the gut	Absorption, first pass required	
	3. What factors contribute to first pass elimination?	Hepatic metabolism Hepatic excretion Gut wall metabolism Portal blood metabolism	Require hepatic metabolism	
	4. What routes of administration other than parenteral can be used to avid first pass metabolism?	Transmucosal Trandermal Rectal	Two required	

Efficacy and Potency	What is meant by the term efficacy? How does efficacy differ from potency? What factors influence the potency of a drug?	a) **Efficacy reflects the limit of the dose-response relation on the response axis.** Determined by the drug's mode of interaction with receptors (eg agonists, partial agonists) or by characteristics of the receptor-effector system. b) **Potency refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug required to provide 50% of that drug's maximal effect.** The clinical effectiveness of a drug depends not on its potency but on its maximal efficacy and its ability to reach its relevant receptors. In considering which of 2 drugs to prescribe, pick the one with the greatest efficacy. Potency can then determine the administered dose. **(c) Potency is affected by the affinity of receptors for binding the drug, and the coupling efficiency.**	

Variation in drug response.	List the factors which contribute to the variation in the response to a drug . Prompt: What mechanisms are involved?	• **Factors include:** – **Age** – **Gender** – **Body mass** – **Disease states** – **Other drugs coadministered** • **Also: tolerance, tachyphylaxis, idiosyncratic reaction.** **(3 of 5)** **4 general mechanisms.** a) **Alteration in concentration of drug that reaches receptor .** (eg altered absorption, altered clearance) b) **Variation in concentration of an endogenous receptor ligand.** (eg propranolol in patients with elevated vs. normal endogenous catecholamines) c) **Alteration in the number or function of receptors** (eg. down regulation → tolerance, overshoot → withdrawal) d) **Changes in response components distal to the receptor** (eg. age, health, disease) **(2 of 4)**	

Bioavailability	What is bioavailability? What factors influence the bioavailability of a drug? (2 out of 3)	a) **Bioavailability is defined as the fraction of unchanged drug reaching the systemic circulation following administration by any route.** eg. IV = 100% bioavailability IM = 75% to <100% Oral = 5% to <100% b) **Factors:** • **Extent of absorption** (eg hydrophilic, lipophilic drugs have poorer absorption eg atenolol) • **First pass elimination** (extraction ratio; F = f x (1-ER) eg morphine 33%) • Rate of absorption (important in single dose regimes eg. hypnotics) Clearance not affected by bioavailability.	

1. Dose - response	What are "spare receptors"? Describe the 2 main mechanisms that account for "spare receptor" phenomenon? What is the effect on the dose-response curve of an agonist with increasing concentrations of an irreversible antagonist?	Receptors in excess of number required for maximal physiol effect Temporal – prolonged effect after transient binding Numerical- limited substrate with excess receptors Curve is shifted to the right with increasing agonist concentrations until eventually only a submaximal effect is achieved	

1. Drug half-life	What is the half-life of a drug? How may it be expressed in relation to other pharmacokinetic parameters? Give examples of factors that affect half-life	Time required to change the amount of drug in the body by one-half during elimination. $T_{1/2} \propto Vd / Cl$ (1 example for Vd and Cl)	

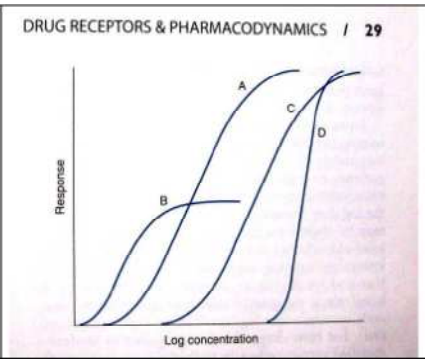
1. Second Messengers	1. Describe the 3 major steps in a second messenger receptor system (3 FOR A PASS) 2. Give 3 examples of ligands that work via a second messenger (3 FOR A PASS)	1. Cell surface receptor for an extracellular ligand 2. Intracytoplasmic activation of a G-protein 3. Activation of an effector (eg adenylate cyclase) with production of the 2nd messenger (eg cAMP) See table 2-1 p22	

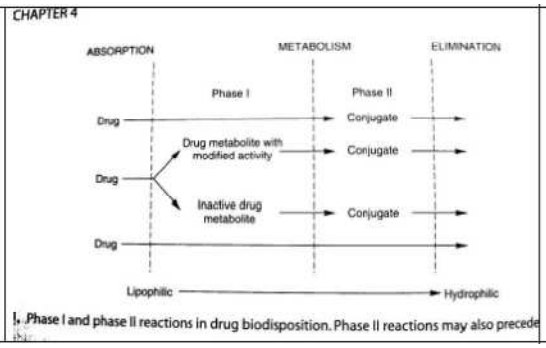
Efficacy and potency	Define potency? How does potency differ from efficacy for a given drug? *PROMPT* What is meant by the term EC 50?	Measure of how much drug required for effect. Defined in terms of concentration or dose required to produce 50% of maximal effect (EC50, ED50) Efficacy is measure of maximum effect of particular drug **DEFINITION +/- GRAPH**	Well illustrated with graph (figure 2-18 in Katzung, p 28)

Volume of distribution	Define volume of distribution? How can a drug have a Vd greater than total body water? Give an example? What are the patient factors that alter Vd?	Amount of drug in body / Concentration in blood (or plasma) **Drugs with high conc in extravasc tissues** Digoxin (500 l), Imipramine (1600 l), Chloroquine (13000 l) Age; disease states Weight; Fat distribution **2 of above**	"Apparent" volume Lots of Choices (Katzumg p37-8) Fluoxetine, nortriptylline, verapamil Mostly a function of body weight, depending of drug may go up or down with age. Alcohol decreases with age, diazepam increases with age (Goodman)

Elimination kinetics	What is meant by the term capacity limited elimination? *Prompt "what is meant by the term zero order kinetics"* Give some examples of drugs with zero order kinetics?	**definition** Phenytoin, Alcohol, aspirin **2 of 3**	Zero order kinetics; Saturable kinetics, non linear Michalis Menten Graph allowed
heparins			

1.1 Volume of distribution	Define the term "volume of distribution" How is it possible for a drug to have a VD of 1600L/70kg? Give me an example of a drug with a: - high VD (>70L/70kg) - low VD (<50 L/70kg, approximating TBW or ECF volume If a drug is distributed in the TBW, what is it's V_D	**Amount of drug in body /concentration in blood or plasma** **Higher concentrations in extra vascular tissues than in blood – e.g. lipid soluble** High (**must get one of bold**): **Morphine**, chloroquine, **digoxin**, clonidine, fluoxitine, **tricyclics**, **β blockers**, **diazepam**, Low/approximating ECF/TBW (**must get one of bold**): **aspirin**, **frusemide**, **antibiotics** (gentamicin, amoxicillin, cephalexin), tolbutamide, **phenytoin**, valproic acid, **lithium**, warfarin **Bold** (particular relevance to EM)– use these to prompt; should be able to designate "high" or "low" VD to pass. TBW: 0.6 L/kg or 42 L/70kg	/2

2.1 Efficacy and potency	Describe the difference between potency and efficacy	**Potency = Amount causing the effect, higher potency has lower EC50 or ED50** **Efficacy = Maximum effect of particular drug**		/2

3.1 Phase I and II reactions	**Describe Phase 1 and Phase 2 reactions**: **What organs are involved?**	See diagram in text of process leading to hydrophilic, more polar, readily excreted compound **Phase 1 makes more polar/reactive, Phase 2 conjugation with polar molecule** Prompt: What are some of the biochemical reactions that characterize phase 1 reactions Oxidation, reduction, hydrolysis Systems eg: MFO such as P450, NADPH Liver, lung, skin, intestinal wall **(must get 2)**	 Phase I and phase II reactions in drug biodisposition. Phase II reactions may also precede	/2

1.1 Routes of Drug administration (JT)	By what different routes can drugs be administered? Discuss the factors affecting absorption from the oral route Give examples of drug administration that bypass the first pass effect	IV, IM, SC, o, rectal, inhalations, transdermal (5 to pass) Incomplete absorption, gut bacteria metabolisim (digoxin), too hydrophilic (atenolol), too lipophilic (acyclovir) Acid-base interactions (aspirin) co ingestants (First pass effect, GIT transit time) reverse transporter All injections, GTN (patches, spray and sublingual tabs), transdermal fentanyl, rectal (partial)	/2

			Score
2.1 First pass effect (BF)	What is the first pass effect?	1 **The reduction in the absorbed dose of a drug that reaches the systemic circulation** (plus 2 or 3) 2 Relates to drugs administered orally and to some extent rectally	
	PROMPTS What factors reduce the amount of an orally administered drug reaching the systemic circulation?	3 Results in reduced bioavailability	
	To which routes of drug administration is it important?	Oral =?- rectal	
	By what mechanisms does the first pass effect occur? **Prompt** Any sites of metabolism other than the liver?	**1 Liver metabolism**. 2 Portal blood metabolism 3 Gut wall metabolism 4 Bile excretion	
	What is the formula for the extraction ratio?	1 ER = CL liver/ Q (Q @ 90L/hr in normal 70kg person)	

3.1 P450 (MS)	What is the role of Cytochrome P450 in drug metabolism? What are the effects of oxidation on the drug? List the basic mechanisms by which Cytochrome P450 enzymes are induced. Give examples ? (1 each).	**Transfers activated oxygen to the drug to form the oxidized metabolite of the drug** • More polar (2 of 3 to pass) • more easily excreted • May be inactivated • Enhancing the rate of synthesis (1 to pass) • Reducing the rate of degradation Enhanced synthesis; Dexamethasone, Phenobarbital Reduced degradation; Clotrimoxazole, ethanol		/2