ACEM PRIMARY 2010.1 PHARMACOLOGY VIVA Thursday Session am *Candidate Number*..... AGREED MARK.....

TOPIC	QUESTION	NOTES	ESSENTIAL KNOWLEDGE
Question 1: Spare receptors & their significance P13-4	1. Define the term "spare receptor"	**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	Highlighted section concept
	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?*	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	concept
Question 2: Antibiotics in urinary sepsis P 732, 755-61, 765-6	1. Describe the mechanism of action of gentamicin ?	Irreversible inhibitor of protein synthesis-possible mechanism: 1. Passive diffusion via porin channels across outer memb, then active transport into cytoplasm by an O2 dependant process. . 2. Binds 30S ribosome & inhibits protein synthesis by 1) Inducing misreading of mRNA thus producing toxic or nonfunctional protein; 2) interfere with initiation complex of peptide formation; 3) cause break up of polysomes into non-functional monosomes.	Irreversible protein synth inhibitor. Binds ribosomes
	2. What are the benefits of once daily dosing ? *Prompt how does this improve clinical effectiveness*	1. *Concentration- dependant killing* (at increased conc kill increased no of bacteria at a more rapid rate; 2. *Postantiobiotic effect*- activity lasts longer than detectable serum levels; 3. *Reduced toxicity* – time above critical level will be longer with multi dose than single dose schedule); 4. Less nursing time; OPD therapy possible; 5. Drug level not required unless >3 day therapy.	Conc dependant kill + 2 others.
	3. How do penicillins enhance the efficacy of gentamicin? *Optional question*	Low ECF pH & anaerobic conditions inhibits transport Transport enhanced by cell wall active drugs eg. penicillin	
Question 3: Aspirin P575-8	1. Describe the pharmacokinetics of Aspirin *What's the significance of it being a weak acid?*	Aspirin has pKa 3.5; Rapidly absorbed from stomach and upper small intestine→peak plasma level in1-2 hrs. Half life: 15 min. Rapidly hydrolysed→Acetic Acid+Salicylate by esterases in tissue and blood. Salicylate non-linearly bound to albumin. Alkalinisation of urine increases rate of excretion of free salicylates and its water soluble conjugates. Small Vd, capacity limited metabolism	Rapid abs, small Vd, renal excretion

	2. What are the adverse effects of therapeautic doses of Aspirin? *What are the respiratory effects of aspirin?* *Are there any other systems affected?*	CNS: Headache, tinnitus, dizziness CVS: Fluid retention, H/T, oedema GIT: Abdo pain, N,V, Ulcers, Bleeding Haem: Thrombocytopenia, neutropenia, Aplastic a Hepatic: Abn LFTs, liver failure Pulmon: Asthma Skin: All types of rashes, pruritis Renal: Impairment and failure, hyperK, proteinuria	GIT + allergy + bronchospasm
Question 4: Amiodarone P228-9	1. What are the cardiac effects of amiodarone at a cellular level?	Prolongs AP duration (by blocking K+ channels) Blocks inactivated Na channels. The AP prolonging action reinforces this effect. Blocks depolarized cells > normal cells. Mild antisympathetic. noncompetitive inhibitor of beta receptors; Weak adrenergic blocker - slows HR and A-V node conduction. Weak Ca channel blocker. Inhibits abnormal automaticity; slows sinus rate; increases PR interval	K block and 1 other
	2. What are the mechanisms of pharmacokinetic drug interaction with Amiodarone and give two examples.	Inhibits liver cytochrome metabolising enzymes Digoxin, Warfarin levels increase. Cimetidine increases amiod toxicity by decreasing hepatic clearance. Interacts with statins (artorvastatin and simvastatin; instead use pravastatin as not P450). Concentration and effects of Phenytoin, anaesthetics, cyclosporins, theophylline, procainamide, flecainide, quinidine are increased by amiodarone	Enzyme induction/inhibition + 1example of either
Question 5: Passive immunisation in ED p1073-8	1. What is passive immunisation?	Giving preformed antibodies to a recipient. Source may be human, animal	Concept
	2. What is passive immunisation useful for?	1. prevention of disease when time does not allow immunisation 2. treatment of disease normally prevented by immunisation 3. for patients unable to form antibodies 4. for treatment of conditions for which active immunisation is unavailable or not possible eg snakebite	2 uses
	3. What passive immunisations might we consider in ED?	tetanus, botulism. measles, rubella, vaccinia, varicella Hep B, Hep A; diphtheria, rabies. antivenoms – spiders, snakes; Rhesus incompatibility	Tetanus + 1 other

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TOPIC	QUESTION	NOTES	ESSENTIAL KNOWLEDGE
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
Question 2: Antibiotics in CNS infections P737-40, 751-2, 790-5, 835	1. How are cephalosporins classified? *What are the differences between the classes?*	1- GPs; 2- + haemophilus & kleb; 3-GP + GN; 4- pseudomonas	1-4 with increasing GN spectrum activity; less GP activity
	2. Why are 3rd generation cephalosporins used in CNS infection?	Expanded GN activity & cross the BBB; penetrate body fluids well; good toxicity profile	Spectrum activity & penetration CNS
	3. Are there any bacteria responsible for CNS infection that cephalosporins do not cover?	Listeria Resistant pneumococci may need vancomycin Resistant E Coli; use with aminoglycoside to cover Pseudom	1 example
Question 3: Paracetamol Toxicity P 591-2, 56-7	1. Describe the mechanism of Paracetamol hepatotoxicity	In normal doses, Paracetamol undergoes glucuronidation and sulphation to the corresponding conjugates, making up 95% of total excreted metabolites. The alternative P450 dependant pathway accounts for 5%. When intake far exceeds therapeutic intake, glucuronidation and sulphation pathways are saturated, so P450 dependent pathway becomes impt. So long as there is hepatic GSH available for conjugation, no hepatotoxicity occurs. Once hepatic GSH is depleted faster than its regeneration, a reactive toxic metabolite-N-acetylbenzoiminoquinone is produced. This reacts with the nucleophilic groups of cellular proteins to produce hepatotoxicity.	concept of 2 paths with saturation Glutathione key word
	2. What is the antidote and how does it work?	NAC glutathione substitute, binding to the toxic metabolite Anti oxidant	NAC + donor/substitute (GSH)

Question 4: Metoprolol P147-55, 169	1. Describe the pharmacokinetics of metoprolol *What's the bioavailability?* *Why is this so?* 2. How does metoprolol differ from propranolol in its action at beta receptors? 3. How do B Blockers control hypertension?	Oral or IV, Well absorbed Bioavailability 50% due to first-pass effect Large volume of distribution Half-life, 3-4 hours Metabolised in the liver B1 equipotent B2 50-100 fold less potent Not fully understood Negative inotropic and chronotropic effects Slow a-v node conduction Antagonises release of renin caused by sympathetic nervous system	Large Vd + first pass B1 selective Negative inotrope/chronotrope
Question 5: Evaluation of drugs and clinical trials Katzung 68-73	1. During clinical drug trials, what factors might confound the results? *What are some of the host factors?* *What are some of the observer factors?* *Why do you blind trials?* 2. What can be done to minimise the confounders?	1. variable natural history of most diseases 2. presence of other diseases and risk factors 3. subject and observer bias 1. large populations over sufficient time; cross-over trials 2. exclusion criteria; randomisation; cross-overs 3. placebo controls; blinding; cross-overs	Bias Bonus points for comment

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TOPIC	QUESTION	NOTES	ESSENTIAL KNOWLEDGE
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
Question 2: Drugs in status epilepticus P374-92	1. Describe how phenytoin is administered in status epilepticus? *What's the mg/kg dose?*	IV load 13-20mg/kg,, given diluted in saline (precipitates in glucose at max rate in adults of 50mg/min Continued 100mg Q6-8hrly	Dose mg/kg, iv route safe rate
	2. Describe the adverse effects of phenytoin ? *What about short term vs long term effects?* *What about in iv administration?*	Dose related nystagmus, ataxia, diplopia long term: gingival hypertrophy, hirsuitism mild facial coarsening & peripheral neuropathy abnormal Vit D levels (osteomalacia) low folate levels; megaloblastic anaemia; Foetal hydantoin syndrome. Idiosyncratic: skin rash; SJ syndrome; Lymphadenopathy; agranulocytosis. Rapid iv may cause hypotension/arrhythmia Drug interactions; reduced CL & binding in neonates	CNS + skin + CVS in iv admin

Question 3: Morphine P489-98	1. Describe the effect of morphine on the different opiod receptors?	Morphine is a full agonist in the μ (mu) receptor→ analgesia, sedation, ↓respirations, ↓ GIT transit, modulation of hormone and neurotransmitter release ; also affects σ (delta) → analgesia, modulation of hormone and neurotransmitter release and Ќ (kappa)→analgesia, psychomimetic effects,↓ GIT transit	Agonist mu receptor + 1 receptor
	2. Describe the effects of morphine on different organ systems?	CNS: Analgesia, euphoria, sedation, respiratory depression; miosis, hyperthermia, -stimulates release of ADH, prolactin and somatotrophin, -truncal rigidity, Resp: depression, Cough suppression, CVS: bradycardia GIT: constipation, contracting biliary smooth muscle, N&V, Renal: Depressed renal function Gynae: Decreases uterine tone Skin: Pruritis, urticaria	CNS + resp + 2 others
Question 4: Atropine P108-9, 114-6	1. Describe the pharmacokinetics of atropine	Oral or IV (usually), neb, topical; Well absorbed orally Widely distributed (including CNS) Half-life 2 hours Elimination: 60% excreted renally unchanged 40% phase I and phase II metabolism and renally excreted	Wide distribution + short t1/2
	2. At which receptors does atropine act?	Muscarinic (equipotent at M1, M2 and M3) Nicotinic (minimal potency)	Predominant Muscarinic
	3. What are the effects of atropine on heart rate?	Lower doses often an initial bradycardia, (Blocks prejunctional M1 receptors); Tachycardia	Dose dependant
Question 5: Therapeutic drug monitoring p46-49	1. What pharmacokinetic variables affect drug levels? *Patient factors?* *Specific drug examples?*	absorption – eg small bowel abnormalities clearance – eg impaired renal, liver, cardiac function volume of distribution – changes in either tissue or plasma binding impact drug availability; eg decreased muscle mass in elderly, hypoalbuminaemia, drug interaction.	2 variables
	2. What pharmacodynamic variables affect drug dosing?	maximum effect (Emax) – vs toxicity by increasing dosing beyond maximum effect sensitivity (EC50) – eg hyperkalemia decreases sensitivity to and effect of digoxin	