ACEM PRIMARY 2008/2 PHARMACOLOGY VIVA Day THURSDAY am *Candidate Number*…… AGREED MARK……

TOPIC	QUESTION	ESSENTIAL KNOWLEDGE	NOTES
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
Question 2: Metronidazole	1. Describe the pharmacokinetics of metronidazole 2. What are the adverse effects of metronidazole?	(Class: Nitroimidazole antiprotozoal drug.) Pharmacokinetics: Well absorbed orally; Oral/IV/suppository (99% oral bio-availability); Metabolised in liver (can accumulate in hepatic insufficiency) and excreted in kidney; Low protein binding (10-20%); Dosage: 500mg tds or single dose of 2g for vaginitis; Half life 7.5 hours Nausea, diarrhoea, dry mouth, hairy black tongue Headache, paraesthesia, dizziness, insomnia Dysuria, dark urine, Disulfiram-like effect, hence avoid alcohol Potentiate the effect of coumarin anticoagulants, Lithium Teratogenic effect on mice, but not proven in human	Need 3 out of 6 PK Need 3 out of 6 categories
Question 3: Tricyclic antidepressants	1. What is the mechanism of action of the tricyclic antidepressants? Prompt: Name one amine? "Where does it happen? 2. Describe the toxic effects in overdose and how are they mediated?	Block amine (NAdr or Serotonin) reuptake pumps at presynaptic nerve endings prolongs duration of action of neurotransmitters at postsynaptic receptors. Most non selective Antimuscarinic. tachycardia, dry mouth, blurred vision, delirium, coma, Agitation; Urinary retention, reduced gastric motility, Respiratory depression; Neuromuscular irritability and seizures Sympathomimetic: tremor. Insomnia Sedation: additive effects alpha1-antiadrenergic – postural hypotension, Hypotension, dizziness fast sodium-channel blockade – reduced myocardial contractility, QT prolongation, cardiac arrhythmias;	Amine block, reuptake inhibitor some antimuscarinic cardiac (mix) Na channel block effects

Question 4: Sulfonylureas	1. What are the mechanisms of action of the Sulfonylureas? Prompt: How do sulphonylureas lower glucose? Describe another mechanism? 3. What are the adverse effects of sulfonylurea therapy?	Increased secretion of insulin - Bind to pancreatic B cell receptor causing increased release of Insulin -Reduced serum glucagon levels – with chronic use thought to be due to indirect inhib effects of insulin and somatostatin on a cells -Potentiation of insulin action on target tissues – increased binding of insulin to tissue receptors ?due to indirect effect of reduced glycemia or FFA levels Prolonged hypoglycemia; Alcohol intolerance – flushing; Dilutional hyponatremia (genetic predisposition) Jaundice, Leucopenia, thrombocytopenia (Chlorpropamide)	Bind to B cell; 1 of other 2 Hypoglycaemia

Question 5: Laxatives	1. Using examples, outline the mechanism of action of the various types of laxative? *Prompt: How does X work for example*	**Irritants or Stimulants** - (act early) castor oil -(act late)cascara, ***senna***, aloes (contain emodin alkaloids which are liberated after absorption from the intestine and excreted in the colon) -(prolonged action by enterohepatic circulation) phenolphthalein & biscodyl **Bulking agents** -hydrophyllic colloids, agar, psyllium seed, ***bran*** **Osmotic** -magnesium citrate and magnesium hydroxide, polyethylene glycol, sorbitol, ***lactulose*** **Stool softeners**: agents that emulsify with the stool and soften it (mineral oil, ***glycerine***, detergents such as docusate (dioctyl sodium sulphosuccinate)	3 out of the 4 mechanisms with at least 1 correct example NB –anything that distends intestine leads to peristaltic activity i.e. bulking and softening agents

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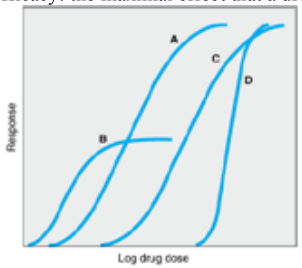
TOPIC	QUESTION	ESSENTIAL KNOWLEDGE	NOTES
Question 1: Efficacy and Potency	1. What is the difference between Efficacy and Potency? Prompt: You can draw a diagram if you like?	Potency: the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of that drug's maximal effect. Efficacy: 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)
Question 2: Cephalosporins	1. How are the cephalosporins classified and give examples? *Prompt:* *What are the different antimicrobial spectrums of the generations?*	1st-gen: (cephalexin, cephazolin, cephalothin) **very active against GPC** (pneumococci, strep, and staph). **GN org** (*E coli, K pneumoniae, & Proteus mirabilis*) **often sensitive**, but not against GN aerobes (*P aeruginosa,* indole-positive proteus, enterobacter, *Serratia marcescens,* citrobacter), & acinetobacter. 2nd-gen: (cefaclor, cefamandole, cefuroxime) **active against organisms inhibited by 1st-gen drugs,** but have **extended GN coverage.** Klebsiellae are usually sensitive. Some anaerobic 3rd-gen agents (cefotaxime, ceftazidime, ceftriaxone) have **expanded GN coverage & X BBB.** Less active against staphyl than earlier cephalosporins but are active against citrobacter, *S marcescens,* & providencia. Also **effective against β-lactamase-producing strains of haemophilus & neisseria.** Some anaerobic None above active against MRSA, enterococci or *P aeruginosa.* 4th see next column	**Know there are 4 generations, and understand principles of 3 of these** 4th-gen: (Cefepime) **extended spectrum of activity covering the majority of the enteric GNRs, including *Pseudomonas* and Enterobacter. Also active against *S aureus,* &*S pneumoniae***. More resistant to hydrolysis by chromosomal β-lactamases (eg, those produced by enterobacter).
	2. What are the adverse effects of the Cephalosporins?	**Hypersens reactions identical to penicillins**: **anaphylaxis, fever, skin rashes, nephritis, granulocytopenia, & hemolytic anemia**. Some individuals with a history of penicillin allergy may tolerate cephalosporins. **Frequency of cross-allergenicity** uncertain, probably around **5–10%.** Severe pain IMI. Thrombophlebitis IVI. **Renal toxicity: interstitial nephritis & ATN**. Cephalosporins with a methylthiotetrazole group (eg, cefamandole, cefotetan) may **cause: hypoprothrombinemia, bleeding** (preventable with Vit K_1 10 mg twice weekly) and **severe disulfiram-like reactions** with alcohol.	Essential penicillin cross reactivity + 2 others

Question 3: SSRIs	1 What is the mechanism of action of the SSRI drugs *Prompt selective serotonin reuptake inhibitors* *Prompt for delayed onset of action- possible mechanisms*) 2 What receptor/channel effects lead to the SSRI side effect profile *Prompt why are SSRIs safer than TCAs?*	i) **Amine hypothesis** – modulation of **NET + SERT** pathways by reuptake inhibition ? > serotonin response ii) Prolonged synaptic exposure to Serotonin leads to iii) prob **time frame 3-6 weeks** due to presynaptic/ post synaptic receptor / storage regulation iv) SSRIs **v HT specific** v TCA 300-7000:1 Very **specific for HT**(partic 1) receptors –therefore **serotonin syndrome/ restlessness. Minimal autonomic** NE activation + mild muscarinic / Na channel, **H1** block effects (**safety/ tolerance**). Possibly some α block (sexual dysfunction)	**General understanding** knowledge of amine hypothesis and b) delayed response c) prob alteration in pre/post synaptic **specific HT + 1 other**, Serotonin syndrome Minimal autonomic = good tolerance/ safety modulation receptors and storage
Question 4: Salbutamol	1). Describe the pharmacokinetics of salbutamol? 2). What are the pros and cons of the different routes of delivery *Prompt: MDI vs nebuliser*	1). Absorption –**complete all routes. Gut** fast, **resp tract slower**- depends on **mechanism delivery - gut 80% with Neb. 2).** Metab/elim- **50% 1st pass** (less if IV) (sulphated- inactive) liver, **rest renal/unchanged. 3). No resp metabolism. 4).** t1/2 3-6hr – prolonged if resp 1.Inhaled- Inhaler/ spacer: targeted/ low dose – minimal systemic ? local effects, co-ordination education; ii) Nebulised- less co-ord required> dose/systemic effects , noisy/frighten children- no benefit in co-ordinated patients 2.Oral- easier in v young/ disabled- longer t1/2, > SE profile, big doses, tachyphylaxis- possible increased deaths 3.IV/IM/SC – useful in asthma extremis or other indications, less 1st pass/. IV- pain/cost/staff use/high SE profile + high risk pts	**good fast absorption- all routes** **Metab 50% + renal.** **Grasp of 2 different routes** Inhaler/ spacer v Neb v IV minimum. Targetted proven effectiveness inhalers/pacers SE profile: < to > Inh v Neb v Oral v Systemic Co-ordination/delivery in extremis (age or severity) important

Question 5: Thioamides	1. How does carbimazole act in thyroid disease? 2. What are the major side effects of carbimazole? 3. How does carbimazole differ from propylthiouracil?	Metabolised to methimazole: **Major action block hormone synthesis** T3 and T4 **Inhibits thyroid peroxidase** – limits organification of iodine. Also blocks coupling of iodotyrosines Small action in blocking peripheral deiodination of T3 and T4. Slow onset as T4 may takes weeks to become depleted Rash maculopapular, pruritus – common; **B one marrow suppression**: neutropenia, agranulocytosis (reversible). Others – urticaria, arthralgia, lupus reaction, vasculitis, jaundice/hepatitis; nausea and GI, occur early **Carbimazole is a prodrug** - converted to methimazole in vivo. Methimazole is 10 times more potent **And one of the areas below** 1. PTU has greater action in inhibiting peripheral deiodination of T4 and T3 2. Propylthiouracil is strongly protein bound: preferred in pregnancy; not secreted in breast milk 3. PTU has shorter half life 1.5 vs 6 hours. PTU given qid, Carbimazole is daily 4. PTU bioavail 50-80%, vs Carb 100% Vd = TBW) 5. PTU excreted in urine as glucuronide metabolite <24 hours, carb in 48+ hours)	Bold to pass 1 side effect Bonus marks

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TOPIC	QUESTION	ESSENTIAL KNOWLEDGE	NOTES
Question 1: P450 enzyme system	1. What is the role of the cytochrome P450 enzyme system? *Prompt: what does CP450 do?* 2. What is the mechanism of CP450 enzyme induction and give examples?	**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+ 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	Bold to pass 1 mechanism and 2 examples
Question 2: Gentamicin	1. Describe the mechanism of action of gentamicin? 2. What are the benefits of once daily dosing? *Prompt how does this improve clinical effectiveness?*	Irreversible inhibitor of protein synthesis. Passive diffusion via porin channels across outer memb, then active transport into cytoplasm by O2 dependant process; transmemebrane electrochem gradient supplies the E, transport coupled ti proton pump. Low ecf pH & anaerobic conditions inhibits transport as reduces gradient; transport enhanced by cell wall active drugs eg penicillin. Binds 30S ribosome & inhibits protein synthesis by simultaneously: 1). Inducing misreading of mRNA thus producing non toxic protein; 2) interfere with initiation complex of peptide formation; 3) cause break up of polysomes into non-functional monosomes Concentration dependant killing (at increased conc kill increased no of bacteria at a more rapid rate; post antibiotic effect (effect lasts longer than detectable serum levels); reduced toxicity (as toxicity is time & conc dependant –time above critical level will be longer with multi dose than single dose schedule); less nursing time; OPD therapy possible; convenience	Irreversible protein synth inhibitor A ribosome inhibitor Conc dependent kill + 1 other

Question 3: Phenytoin	1. Describe the pharmacokinetics of phenytoin?	Weak acid pKa 8.3; oral abs almost complete 90%, with peak serum conc 3-12hrs later. Slow release formulation also. IMI: incomplete abs with drug precipitation in the muscle, fosP OK **Highly plasma protein bound,** metabolised to inactive metabolities with urinary excretion, < 2% exc unchanged in urine. **Dose dependant kinetics**; Vd 45L/70kg. t1/2 av 24 hours (conc dependant). Therapeutic level 10-20mg/L. Drug interactions via plasma protein binding or via enz induction (CYP2C19 & CYP2C9). Alters TFT results; reduced CL neonates; foetal hydantoin syndrome	Pass: highly protein bound and dose dependant kinetics
	2. Describe the pharmacodynamics of phenytoin? *Prompt: what is the effect on action potentials?*	**Block sodium channels** & inhibits the generation of repetitive APs blocks sustained high frequency repetitive firing of APs). Preferential binding to & prolongation of the inactivated state of the Na channel (use dependant effect on Na conductance). **Other electrolyte effects** -alters K conductance; alters Ca conductance ad decreases Ca permeability, inhibits Ca influx therefore affecting neurotransmitter & hormone release; -interacts with membrane lipids ? stabilising membranes; -paradoxical excitation in some neurones; -alters membrane potentials and the conc of amino acids; affects neurotransmitters NA, Ach & GABA. High conc inhibits serotonin and NA release, promotes uptake of DA & inhibits MAO activity.	Pass: Na channel, And one other effect
Question 4: Metoclopramide	1. Describe the mechanism of action of metoclopramide? *Prompt: what receptor does it act on?* *What are the peripheral/central actions?*	**Dopamine antagonist** (D2 receptors) **Central** – via anti - nauseant and anti - emetic effect on the Chemoreceptor Trigger Zone (area postrema) **Peripheral** – blockade of GI dopamine receptors allowing cholinergic smooth muscle stimulation - increases oesophageal peristaltic amplitude - increases lower oesophageal sphincter pressure - enhances gastric emptying	Pass dopamine antagonist, peripheral & central action
	2.. List the adverse effects of metoclopramide?	Relate to central dopamine antagonist action - restlessness, drowsiness, insomnia, anxiety, agitation - **extrapyrimadal effects** – dystonias, akathisia, parkinsonian features. - risk of tardive dyskinesia with chronic use - hyperprolactinemia (galactorrhoea, gynecomastia, impotence, menstrual disorders)	Extrapyramidal + 1
Question 5: Flecainide	1. What is flecainide's mechanism of action?	**Na channel blockade** (class effect). Predominant action is to inhibit the fast, or sodium, channel which is largely responsible for the rapid upstroke of the myocardial action potential in cardiac conducting tissue **Class 1C action** - – minimal effect on the Action Potential Duration and dissociates from the Na channel with slow kinetics. (no effect on QT interval) Decrease the rate of rise (V_{max}, phase 0) of the action potential with little effect on duration.	Na channel block, class 1C
	2. Describe flecainide's pharmacokinetics. **Prompt** Usual oral dose Tambocar trade name	Well absorbed orally, half life ~ 20 hours, Peak plasma drug levels at ~ 3 hours (range 1-6 hrs), Vd ranges from 5 to 13.4 L/kg (mean 8.7 L/kg), 30% of a single oral dose (range 10 to 50%) is excreted in urine as unchanged drug – remainder by hepatic metabolism. Usual dose 100- 200 mg daily	2 things
	3. In which patients is it contraindicated?	Hypotension, LV dysfunction	Any answer