GI/NSAIDs/Paracetamol VIVAs (Pharmacology)

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2014.2A

Question 2 Proton Pump Inhibitors (pp 1085-1089) **Subject:** Pharm LOA: 2	1. Describe the MOA of PPIs	**Irreversibly inactivates H^+K^+ATPase**, blocking the proton pump-inhibiting >90% acid secretion, for up to 24 hrs (time taken for synthesis new enzymes).	Bold to pass.
	2. Why is an IV infusion preferred to a single bolus dose?	**Only inactivates actively secreting acid pumps** (<10% in fasting patients). Hence single dose only decreases acid secretion for a few hours.	Bold to pass.
	3. Regarding oral formulations of proton pump inhibitors, please describe strategies used to increase their bioavailability and activity.	Taken as **inactive pro-drugs**, Begin as **acid resistant enteric coated** to prevent gastric elimination. Take on **empty stomach** as food decreases bioavailability. Weak bases so pass into acidified parietal cells, where concentrated 1000x, ecomes activated and binds to H^+K^+ATPase. **Take 1 hour prior to meal** so peak dose drug occurs when most pumps are active.	2 concepts.

2014.1D

Question 1 Bioavailability with particular reference to NSAIDs **Subject:** Pharm LOA: 1	(a) What is bioavailability?	(a) Fraction of **unchanged drug** reaching the **systemic circulation** following administration by any route	(a) Bold to pass
	(b) What factors affect bioavailability?	(b) 3 factors: **Extent of absorption** • Too hydrophilic or too lipophilic – decr. absorption • Reverse transporter associated with p-glycoprotein – pumps drug back to gut lumen – decr. absorption • Gut wall metabolism – decr. absorption **First pass metabolism** • Metabolism by liver before it reaches systemic circulation • Small additional effect if drug has biliary excretion Rate of absorption • Determined by site of administration and drug formulation	(b) Bold with reasonable explanation of each
	(c) What is the bioavailability of ibuprofen?	(c) **High** - Weak organic acid – **well absorbed rapidly. Minimal first pass metabolism**	(c) Bold to pass

2013.2B

Question 3 PHARMACOLOGY LOA: 1	1. Moving on to pharmacology. What is the mechanism of action of the non steroidal anti – inflammatory drugs (NSAIDs)?	NSAIDs serve to suppress inflammation chiefly by **inhibiting prostaglandin synthesis.** In so doing they decrease the sensitivity of vessels to bradykinin and reverse the vasodilation of inflammation. Cyclo – oxygenase (COX) is the key catalyst for arachidonic acid conversion to prostaglandins. **NSAIDs inhibit COX**, thus inhibiting this conversion.	**Pass criteria** Inhibit COX, thus decrease prostaglandin synthesis – and in so doing the response to inflammation is modulated. **Irreversible vs reversible**
	2. How does aspirin differ from other NSAIDs in its action on COX?	**Aspirin** (original NSAID) **irreversibly inhibits COX**, whilst the **newer NSAIDS** (ibuprofen, diclofenac) **reversibly** inhibit COX.	
	2. What are the adverse effects of NSAIDs?	2 types of COX exist – COX 1 is expressed in most cells, and COX 2 is inducible, its expression varies depending on stimulus. Selective COX 2 inhibitors (celecoxib) do not affect platelet function at usual doses, whilst the other NSAIDs do inhibit platelet aggregation. **GI EFFECTS** – GI irritation, ulcers, abdominal pain, N and V **BLEEDING** – secondary to platelet effects **RENAL** – nephrotoxicity, hyperkalaemia ALLERGY – rash, pruritis **CARDIOVASCULAR** – Selective COX 2 inhibitors - implicated in increased risk of c'vasc thrombotic events, - fluid retention, oedema, hypertension CNS – headaches, tinnitus, dizziness, stroke PULMONARY – asthma HAEM - rare – t'cytopaenia, neutropaenia HEPATIC – abnormal LFTs	**¾ Bold plus one other to pass** – namely – GI effects, bleeding, and renal effects…plus any one of the others

2013.1.1

Question 5 **N-ACETYLCYSTEINE** LOA: 2	What is the mechanism of action of N-acetylcysteine in paracetamol overdose?	Paracetamol metabolism by hepatic glucuronidation/sulphation is saturated resulting in increased metabolism via cytochrome p450 system to form N –acetylbenzoquinoneimine (NAPQI), a **toxic intermediate**. Elevated NAPQI production leads to depletion of hepatic glutathione stores, resulting in hepatotoxicity. NAC prevents paracetamol induced hepatotoxicy by 4 possible mechanisms: 1) **Increased glutathione availability**/Sulfhydryl donor 2) Direct binding to NAPQI 3) Provision of inorganic sulphate 4) Reduction of NAPQI back to paracetamol	**Bold to pass**
	Name an adverse effects of N-acetylcysteine.	Mild **anaphylactoid reactions**(15-20%)- mild flushing, rash and angio-oedema.	**Bold or description**

2013.1.2

Question 5 **OCTREOTIDE** LOA: 2	What are the therapeutic uses for octreotide?	Control of **bleeding gastro-oesophageal varices,** sulphonylurea induced hypoglycaemia, pituitary and carcinoid tumors.	**Bold to pass**
	What is the mechanism of action of octreotide in acute variceal bleeding?	**Reduces splanchnic blood flow/portal venous pressure.** Exact mechanism of how this occurs is not known.	**Bold to pass**
	How is it administered in acute variceal bleeding?	**IV bolus and infusion** (50mcg bolus then 25-50mcg/hr) or SC	**Bold to pass**
	Why is an infusion required?	**Short half-life**	**Bold to pass**

2012.1.1

Question 4 LOA: 1 **ANTIEMETICS**	Name some antiemetics used in the Emergency Department.	**Ondansetron (or Granisetron or Tropisetron)** **Metoclopramide** **Prochlorperazine** Diphenhydramine (or other antihistamines). Meclizine. Hyoscine. Benzodiazepines. Chlorpromazine. Droperidol	Bold to pass
	Compare the mechanisms of action of ondansetron and metoclopramide	Act at different receptors: Ondansetron: **Peripheral 5HT3 blockade** (vagal and spinal afferents, Reduces sensory visceral output) + Central 5HT3 blockade (vomiting centre and CTZ) Metoclopramide: **D2 blockade** (CTZ). Increases oesophageal motility. Increases LOS pressure. Increase gastric emptying	Bold to pass
	Describe the potential adverse effects of metoclopramide.	CNS: Restlessness, drowsiness, insomnia, anxiety, agitation – common (20%), esp. elderly Extrapyramidal effects: **acute dystonia**, akathisia, parkinsonian effects, more likely with higher doses Tardive dyskinesia with chronic dosing	Must mention acute dystonia + one other CNS effect

2012.1.3

Question 2 LOA: 1 **PARACETAMOL**	Describe the metabolism of paracetamol? *Prompt: Does this change in toxic doses?*	Rapidly absorbed, peak conc at 30-60 minutes Slightly PP bound Partially metabolised by hepatic MEs to paracetamol glucuronide and sulphate (inactive) <5% excreted unchanged Half-life is 2-3 hrs	3 of 5
	What is the toxic dose and how does this cause toxicity?	150-200mg/Kg or >7g in adult. Conjugation AAs (gluthathione in particular) used up, metabolised to toxic metabs NAPQI. Toxic to liver / kidneys.	Reasonable approximation. Must have reasonable understanding of how toxicity is caused
	What are the clinical manifestations of toxicity?	GIT effects: **Hepatic** impairment. N/V, diarrhoea, abdo pain, dizzy, disorientation Renal failure	Hepatic + one other

2010.1.2

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)

2009.2.3

Question 2: **Side effects of NSAIDs**	(a) What are the side effects of the non-steroidal anti-inflammatory agents?	**Allergy;** rash; pruritis Nausea, abdominal pain, diarrhoea **GI irritation / ulcers** **Bleeding secondary to inhibition of platelet aggregation** **Nephrotoxicity** Peripheral oedema; fluid retention Headache	3 bold to pass
	(b) What specific side effects occur with aspirin?	Salicylism – vomiting, tinnitus, hearing loss and vertigo Exacerbation of asthma Histamine induced flushing Irreversible platelet inhibition Raised LFTs	Any 2 to pass

2008.2.1

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, ***glycering***, 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

2008.1.1

Octreotide	Explain the rationale for the use of octreotide in upper gastrointestinal bleeding What are the pharmacokinetic differences between octreotide and somatostatin? (Supp Question – What other agents may be useful in the prevention and treatment of upper GI bleeding)	Octreotide reduces splanchnic blood flow, (? By glucagon release inhibition) therefore reduces portal venous pressure. This reduces blood loss from bleeding oesophageal varices and in some cases of severe duodenal ulcer related bleeding. Octreotide is a somatostatin analogue that has a longer half life than somatostatin (1.5hrs vs 3 min) so can be given as an IV infusion or subcutaneously. (Pass – reduces splanchnic blood flow)	

Older

COX2 inhibitors	Describe the mechanism of action of the COX-2 selective inhibitors. What adverse effects can be associated with the use of COX-2 selective inhibitors? What other drugs are inhibitors of the cyclooxygenase enzyme system?	**Inhibits prostacyclin synthesis by selectively binding to and blocking the active site of the COX2 isoenzyme.** • **Renal toxicity** • **GIT but fewer than non selective NSAIDs** • **Possible increased CVS thrombotic events.** (2 of 3) **Aspirin** **Non steroidals**	

Paracetamol	Describe paracetamol metabolism Describe the mechanism of toxicity of paracetamol	Hepatic, sulfation/glucuronidation, small amount by P 450 alternative pathway Hepatotoxic metabolite in setting of glutathione depletion	

1.3 Paracetamol (JT)	Describe the pharmaco-kinetics of a single dose of oral paracetamol How is paracetamol eliminated from the body? Describe the mechanism of liver damage caused by paracetamol toxicity	Peak 30- 60 min, slightly prot bind Liver metabolised via microsomal enzymes, (sulphate and glucuronide) 5% hydroxylated and conjugation with glutathione/cysteine via P450 (< 5% excreted unchanged), N ac benzoiminoquinone reacts with sulphhydryl groups on proteins. (Prevention using N ac cysteine)	/2

Question 3: Paracetamol Toxicity P 591-2, 56-7	1. Describe the mechanism of Paracetamol hepatotoxicity 2. What is the antidote and how does it work?	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. NAC glutathione substitute, binding to the toxic metabolite Anti oxidant	concept of 2 paths with saturation Glutathione key word NAC + donor/substitute (GSH)

Antiemetics	What clarrrrsses of drug can be used as antiemetics ? List and explain the adverse effects of prochlorperazine ?	(1) Serotonin 5-HT3 antagonists: the "trons" (2) Phenothiazines: prochlorperazine, promethazine (3) Butyrophenones: haloperidol (4) Substituted benzamides: metoclopramide (5) H1 antihistamines: diphenhydramine (6) Anticholinergics: hyoscine (Benzos, Cannabinoids, Corticosteroids) Acute dystonia (dopamine blockade) Sedation (antihistamine effects) Anticholinergic effects (antimuscarine effects) Allergy	Name three groups to pass – if name agents, prompt for group or mechanism of action. Acute dystonia + one other to pass

Antiemetics	List the major categories of antiemetic agents. (3 of 7) Describe the mechanism of action of three of these. (2 of 3)	**Antihistamines** Diphenhydramine, hydroxyzine - antimuscarinic and sedative effects + H1 blocking effect - effective for nausea and vomiting associated with motion sickness - specific depression of conduction in vestibulocerebellar pathway Anticholinergics (scopolamine) – also useful **Phenothiazines** Prochlorperazine, promethazine - Block dopamine receptors in chemoreceptor trigger zone - use limited by degree of sedation - also cause extrapyramidal symptoms esp.dystonias **Metoclopramide** Dopamine antagonist – enters CNS + 5HT4 agonist action Releases Ach from cholinergic neurons in enteric nervous systems myenteric plexus + may sensitize intestinal sm.muscle cells to action of Ach Not increase gastric or pancreatic secretion Hasten esophageal clearance, raise lower esophageal sphincter pressure, accelerate gastric emptying, shorten sm.bowel transit time **5-HT inhibitors** Odansetron, granisetron and dolasetron – equal efficacy, adverse reactions, Convenience of administration, cost Very effective controlling acute nausea and vomiting assoc. with ordinary dose chemo, leff in delayed emesis and that from high dose cancer chemo new class, neurokinin antagonists under investigations **Marijuana derivatives** – tetrahydrocannabinol (THC) effective in some patients dronabinol – receptors in the chemoreceptor trigger zone **Steroids** = dexamethasone – mechanism unknown **Sedative hypnotics** = benzodiazepines can control anticipatory nausea and vomiting	Rapidly absorbed, peak concentration at 40-120 minutes T ½ 2-4 hours Usual dose 10mg qid with meals, meadtime 1-2mg/kg for cancer chemotherapy Side effects = somnolence, nervousness, dystonic reactions

3. Ondansetron	How does ondansetron work as an anti-emetic? **What are the routes of administration and dose of ondansetron?**	5-HT3 antagonism (gut and brain / central) **Similar doses 4-8 mg oral – tablet/wafer, IV**	

Question 3 Ondansetron	1. What is the mechanism of action of ondansetron?	selective 5-HT_3 receptor antagonists both peripheral in intestinal vagal afferents and central in chemoreceptor trigger zone and vomiting center in lateral medulla	Pass: serotonin
	2. What are the clinical uses of ondansetron?	a) Chemotherapy –induced nausea and vomiting eg 8 mg every 8 -12 hours b) Postoperative and post radiation nausea and vomiting. c) Other indications: acute or chronic medical conditions or gastroenteritis – not well evaluated	2 out of 3
	3. Name some side-effects of ondansetron?	Headache, dizziness and constipation. Small prolongation of QT interval	Pass: 1

Question 4: Metoclopramide	1. Describe the mechanism of action of metoclopramide? *Prompt: what receptor does it act on?* *What are the peripheral/central actions?* 2.. List the adverse effects of metoclopramide?	**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 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)	Pass dopamine antagonist, peripheral & central action Extrapyramidal + 1