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Aspirin 2015-1-D

Stem: A 70 yo woman calls an ambulance for chest pain. She is administered Aspirin en route to hospital. We will start with Pharmacology			
TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Question 1 Aspirin **Subject:** Pharm LOA: 2	1. Outline the mechanisms of action for aspirin.	**Irreversible** non-selective **cyclooxygenase inhibition** (Cox 1 and 2) resulting in (a) In platelets irreversible **inhibition of COX 1 results in reduction in** thromboxane A2 and **inhibition of platelet aggregation** for the life of the platelet (10 days), (b) **In tissues inhibits prostaglandin synthesis** (COX2). Results in **anti-inflammatory action,** Analgesic, and antipyretic effects.	Bold Need to mention platelet effect (Cox1) **AND** tissue (COX2) anti-inflammatory or analgesic effect.
	2. Describe the pharmacokinetics of aspirin.	Rapidly absorbed from stomach and intestine, aspirin hydrolysed to salicylic acid in plasma and blood, peak plasma level within 1-2 hrs. Serum half- life of aspirin 15 minutes, low protein binding, **saturable metabolism with increasing doses (switches from first to zero order metabolism).** Urinary alkalinisation increases excretion of salicylate and it's conjugates.	Bold plus 2
	3. Outline the adverse effects of aspirin.	GI upset, **Gastrointestinal bleeding from gastritis or peptic ulceration,** hepatotoxicity, hypersensitivity reactions (asthma, angioedema, rash), prolonged bleeding time from platelet inhibition.	Bold + 1 other.

Aspirin 2010-1

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

Aspirin 2007-2

3.3 Aspirin (BD)	What is the mechanism of action of aspirin?	**Irreversibly inhibits cyclooxygenase** (COX I and II) – reduces prostaglandin synthesis from arachidonic acid	
	Describe what happens to aspirin in the gut following oral administration.	**Highly soluble in acid environment of stomach as it is a weak acid** (rapidly absorbed) Becomes much less soluble (100 times less) in the alkali environment of the upper small bowel **Most of administered dose is absorbed in the small bowel** (due to vastly increased surface area) Possibility of formation of concretions/bezoars	
	How is aspirin eliminated from the body?	Hydrolysed by tissue esterases to salicylate and acetic acid salicylate conjugated with glucuronide or glycine to form salicyuric acid **first order kinetics at low doses - zero order kinetics at higher doses** Then renally excreted – **pH dependent resorption**, amount excreted related to urine volume	
	What are the adverse effects of aspirin? (three to pass)	Asthma – leukotriene production Bleeding – inhibition of thomboxane production in the platelet Peptic ulceration – reduction of PGE1 and PGI2 that increase gastroprotective mcous production by the gastric mucosa CNS – tinnitus, nausea, vomiting, seizures, respiratory alkalosis – direct CNS toxicity Metabolic acidosis – uncoupling of oxidative phosphorylation Allergy – idiopathic Renal failure – inhibition of PGE1 production in renal medulla	/2

Aspirin 2003-2

Aspirin	1. With regard to aspirin, what are its pharmacokinetic properties?	**pKa 3.5**. **Rapidly absorbed** from **stomach** and upper small intestine. **Peak levels at 1-2 hours**. ASA is absorbed as such; hydrolysed in blood to salicylate and acetate. **Bound to plasma protein**; saturatable, therefore increased free ASA with increased plasma concentration. **Saturatable metabolism and excretion; zero order**. $t_{½}$ for 600mg ~ 3-5 hours $t_{½}$ for 3.6g ~ 12-16 hours. Has active metabolite with long $t_{½}$ (12 hours). **Alkaline urine increases ionized free salicylate excretion.**	**4 out of 6 bold items required to pass.**	
	2. What are its adverse effects? Prompt: What are its toxic effects in overdose?	**GIT upset; gastritis; ulceration** (? due to reduced protective PG synthesis) Abnormal LFTs; hepatitis **Bleeding.** **Allergy.** **Salicylism**: - Vomiting; tinnitus; vertigo; loss of hearing Tachypnoea Fever Dehydration Metabolic acidosis Hyperglycaemia Clotting disturbance CVS collapse Renal & respiratory failure Coma	**2 out of 3 bold items plus 5 out of 10 of "Salicylism " effects to pass.**	
	Supplementary question. What are its therapeutic indications?	TIAS Acute coronary syndromes Pre-thrombolysis Anti-inflammatory Analgesia Anti-pyretic		

Colchicine 2007-2

1.4 Agents for gout (AS)	1. Describe the mechanism of action of colchicine (1 and 3 to pass) Prompt - Does colchicine have an effect on uric acid?	1 anti-inflammatory effect (binds to tubulin, inhibits WBC migration and phagocytosis) 2 inhibits formation of leukotriene B4 3 No effect on uric acid metabolism	
	2. What are the indications and dosage of colchicine? (either 1 or 2 to pass)	1 treatment of acute episodes (0.6-1.2 mg 12h until pain reduces or diarrhoea- 8mg fatal) 2 prophylaxis of recurrent episodes (0.6 mg od-tds) 3 (bonus) preventing Mediterranean fever, treating sarcoid arthritis and hepatic cirrhosis	/2

Cox 2 Selective Inhibitors 2005-1

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**	

Fentanyl 2016-1-B

Stem: A 75 year-old man injured his lower limb after a fall. Starting with Pharmacology: He was given fentanyl by the paramedics.			
TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Question 1 Fentanyl LOA: 1	*a. Describe the mechanism of action of fentanyl.*	Synthetic opioid that acts on the **μ receptor.**	Bold
	b. Describe the pharmacokinetics of fentanyl.	**High first pass metabolism, duration of action 1-2 h**, metabolised by P450 CYP 3A4 with no active metabolites. Transdermal, mucosal and IM absorption are good. Fentanyl may be given IV, IM, IN, SC, SL/buccal (with lozenge), transdermal patch, epidural.	Bold plus 2 routes.
	c. Describe its potency relative to morphine	100 times more potent. 0.1mg fentanyl = 10mg morphine	Range 100 to 200.
	d. List the adverse effects of fentanyl.	Respiratory depression, nausea, vomiting, dysphoria, cough, sedation, constipation, urinary retention, itch, urticaria, chest wall & laryngeal rigidity.	Name 4

Fentanyl 2014-1-D

Stem: A 30 yo man presents with a suspected dislocated right shoulder. He is given IV opiates. The first topic is **PHARMACOLOGY**.

TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Question 1 Potency & efficacy with reference to morphine / fentanyl **Subject:** Pharm LOA: 1	(a) What is drug potency? (b) Draw and explain dose-response curves comparing morphine with fentanyl. (c) What are the pharmacokinetics of fentanyl?	(a) **Dose or concentration to achieve 50% maximal effect** (EC_{50} or ED_{50}) (b) **Must graph dose or log dose (X axis) versus response (Y axis).** (c) Highly lipid soluble, Half-life 5 mins, duration 1-1.5 h, low bioavailability, hepatic metabolism	(a) Bold to pass (b) Display differences and explain on graph (c) 3 of 5 to pass

Ibuprofen 2014-1-D

Stem: You have a 25 yo man with a painful knee. He has received ibuprofen for analgesia. The first topic is **PHARMACOLOGY.**

TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
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

Morphine 2015-2-C

Stem: A 60 year old lady presents to ED with a painful arm following a fall.			
TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Stem: She has significant pain and is given morphine			
Question 1 Morphine **Subject:** Pharm LOA: 1	1. What is the mechanism of action of morphine?	**Act on receptors: mu**/delta/kappa **Reduce presynaptic neurotransmission (esp glutamate)** **Inhibit post-synaptic neurons** Central (thalamic action)	Mu + 1 other mechanism of action to pass
	2. Why do opiates cause respiratory depression?	**Inhibition of brainstem respiratory controls** allowing less response to hypercapnoea	Bold to pass
	3. How is morphine metabolised?	**Conjugated in liver** (morphine-3-glucuronide = most) Small amount (10%) morphine-6-glucuronide = increased analgesic potency Renal excretion	Bold to pass

Morphine 2014-1-B

Stem: Moving now to your pharmacology question. You decide to give this patient morphine for analgesia.			
Question 3 Morphine (Katzung 12th edition pp543-556) – pharmacokinetics; pharmacodynamics – in particular, receptors bound to; adverse reactions **Subject:** Pharm LOA: 1	1. What is its mechanism of action? 2. How is morphine metabolised and excreted? 3. What are the possible acute adverse reactions with morphine? Prompt: why are we more cautious in using morphine in renal failure patients?	**1**.Brain and Spinal cord **receptors: mu, delta, kappa.** (Subtypes: 2 mu and delta, 3 kappa). Binding to receptor (particularly mu) >> **reduction of neurotransmitter release from presynaptic nerve terminals** (especially glutamate), and **inhibit postsynaptic neurons** (by opening K channels).Central thalamic action and activation of descending inhibitory pain neurons. **2.** Mostly liver conjugated to morphine-3-glucuronide which has neuroexcitatory properties. 10% is metabolised to morphine-6-glucuronide with 4-6x increased analgesic potency. Excreted renally. **3. Sedation/ resp depression, nausea and vomiting**, hypotension if predisposed, histamine release, dysphoria, biliary colic, pruritis, allergy. In renal failure it can cause seizures, or prolonged analgesia.	Must name mu and 1 other types of receptors, and the 2 bold actions. Liver metabolism & metabolites are renally excreted Bold and 2 more.

Morphine 2012-2

Question 2	Describe the central nervous effects of	1) central	**Bold to pass**
Morphine LOA: 1	Morphine	• **analgesia** • euphoria • **sedation** • **respiratory depression** • cough suppression • miosis • truncal rigidity • nausea / vomiting • temperature	candidate should be able To describe in detail of each one in bold
	Describe peripheral effects?	2) peripheral: • **cardiovascular** • GI- **constipation** • Biliary • Renal • Uterus • Neuroendocrine • Pruritis • immune	

Morphine 2010-1

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

Morphine 2007-2

2.3 Morphine	How is Morphine metabolised?	Converts to polar metabolites in form of glucuronides in liver Primarily conjugated to morphine-3-glucuronide (M3G)→neuro-excitatory properties. 10% of morphine conjugated to morphine-6-glucuronide (M6G)→analgesic effect	
	What opioid receptor sites does it act on?	Full agonist at μ receptor. But also acts on κ and δ receptor sites	
	What is the mechanism of action at the cellular level?	By binding to specific G protein-coupled receptors in brain and spinal cord 1. Close voltage-gated Ca channels → ↓ Ca influx on presynaptic nerve terminals and ↓ transmitter release 2. Hyperpolarise postsynaptic neurones by ↑ K conductance → inhibitory postsynaptic potential	

NSAIDs 2017-2-A

Stem: Moving onto Pharmacology. She is given Ibuprofen to help treat her pain			
Question 5 NSAIDS **Subject**: Pharmacology LOA: 2	a) Describe the pharmacokinetics of ibuprofen. b) Describe the pharmacodynamics of Ibuprofen. c) What are the side effects of NSAIDs?	a) NSAIDs well absorbed, food does not substantially change their bioavailability. Highly protein bound Highly metabolised by liver – Cytochrome P450. b) I**nhibition of prostaglandin biosynthesis.** Additional possible mechanisms of action, including inhibition of chemotaxis, down-regulation of interleukin-1 production, decreased production of free radicals and superoxide, and interference with calcium-mediated intracellular events. **NSAIDs are reversible inhibitors of COX** **Anti-inflammatory, antipyretic and analgesic**. c) Central nervous system: Headaches, tinnitus, and dizziness. CVS: Fluid retention, hypertension, oedema, and rarely, myocardial infarction, and congestive heart failure. **GIT:** Abdominal pain, dyspepsia, nausea, vomiting, ulcers or bleeding. **Renal**: Renal insufficiency, renal failure, hyperkalaemia, and proteinuria. Haematologic: Rare thrombocytopenia, neutropenia, aplastic anaemia. Hepatic: Abnormal liver function tests and rare liver failure. Pulmonary: Asthma. Skin: Rashes, all types, pruritus.	2 to pass Bold to pass At least 4 side effects (must include renal and GIT)

NSAIDs 2013-2-B

Question 3 PHARMACOLOGY LOA: 1	1. Moving on to pharmacology. What is the mechanism of action of the non steroidal anti – inflammatory drugs (NSAIDs)? 2. How does aspirin differ from other NSAIDs in its action on COX?	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. **Aspirin** (original NSAID**) irreversibly inhibits COX**, whilst the **newer NSAIDS** (ibuprofen, diclofenac) **reversibly** inhibit COX.	**Pass criteria** Inhibit COX, thus decrease prostaglandin synthesis – and in so doing the response to inflammation is modulated. **Irreversible vs reversible**
	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

NSAIDs 2009-2

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

Cyclo-oxygenase Inhibitors pp 312-3, 597-607		Aspirin Steroidal anti-inflammatory drugs via COX 2 NSAIDS: Non selective COX-1 and COX –2 inhibitors COX 2 selective agents: Celecoxib & Rofecoxib	To pass: Must volunteer aspirin and NSAID's and mention COX-1 & COX 2 inhibition	
		Alteration and inhibition in the biosynthesis of prostaglandins but also may: inhibit IL-1 Inhibit chemotaxis Decrease production of free radicals Interference with calcium mediated intracellular events **1.Antipyretic** [PGE1 and PGE 2] **2. Anti-inflammatory** [complex:COX-2 inhibition more important] **3.Analgesic** [peripherally via effects on inflammation] **4.Reversible anti-platelet effect**[TXA_2] **5.Inhibtion of gastric cytoprotection**[PGE_1 and E group] **6.Renal impairment**[PGE_1 and PGE_2 and PGI_2 increase GFR through vasodilation **7. Effects on smooth muscle**: inhibit vasodilation, bronchodilation[PGE_2] 8. Closure of PDA[PGE_1 & PGE_2] 9.All NSAIDS are roughly equally efficacious –there is no best NSAID for all patients	To pass: Must get 4/7 bold items via the inhibition of prostaglandins. Bonus marks if able to comments on specific prostaglandins inhibited or processes involved.	
		<u>Common or Common to group</u> **Allergy** Anaphylaxis Angioedema **Asthma exacerbation** [Nasal polyps association] Gastritis Peptic ulceration **GI bleeding** Increase bleeding tendency **Renal impairment especially if dehydration, elderly or pre-existing renal disease is also present** Nausea and vomiting Peripheral oedema Pregnancy –fetal PDA closure <u>Some NSAID.s</u> Hepatic impairment Agranulocytosis Aplastic anaemia Thrombocytopaenia Neurlogical –various Headaches Diarrhoea Pancreatitis Pseudoporphyria	To pass: a good understanding of the common adverse effects. Must get bold items.	
		Less gastric irritation and no inhibition of platelet aggregation with COX-2 inhibitors	To pass: Must get 1/2	

Opioid Addiction 2011-2

Question 5 Addiction & drugs used in opiate addiction	a) Name some drugs that are used in the treatment of opiate addiction b) Outline the principles of how these agents work	**a) Methadone**, N acetylmethadol, buprenorphine clonidine, lofexidine, Naltrexone, naloxone *b) Methadone* –longer acting, opiate angonist, orally active –patient can be stabilised and gradually withdrawn but addictive also. *N acetylmethadol* –an even longer acting methadone analogue. *Buprenorphine* –partial opiod antagonist that can be given once daily, low doses for detoxification and higher doses for maintenance. *Clonidine* –central acting sympatholytic agent that mitigates signs of withdrawal sympathetic Overactivity. *Lofexidine* –clonidine analogue with less hypotensive effects *Naltrexone*-long acting orally active pure opiod antagonist, patients must be detoxified first Naloxone – rapid onset pure antagonist, short half-life, precipitate withdrawal	Must get methadone and 1 other Must get methadone principles and state that overall agents must be orally active and long acting. 1 other agents PD also.

TOPIC: OPIOID ANALGESIA _____ NUMBER: 3

OPENING QUESTION	**Describe the clinically important pharmacological differences between morphine and fentanyl**	**COMMENTS**
POINTS REQUIRED	1. Morphine (a phenanthrene) is naturally occurring. Fentanyl (a phenylpiperidine) is synthetic	
	2. RECEPTOR EFFECTS: – Both are strong agonists (all receptors), but potency fentanyl > morphine	
	3. ABSORPTION – Both morphine & fentanyl have low oral:parenteral potency ratios	
	4. ELIMINATION – elimination t½ morphine > fentanyl	
PROMPTS	"Try dividing your response into the categories of receptor effects, absorption, and elimination."	2 of 3 differences to pass
SECOND QUESTION (if needed)	**How does methadone differ from morphine and fentanyl?**	
POINTS REQUIRED	PD: Methadone also blocks NMDA receptors and monamine reuptake, which may explain its ability to relieve difficult-to-treat pain.	
	PK: Methadone has a high oral:parenteral potency ratio -Elimination t½ methadone >> morphine>fentanyl – Methadone has highly variable (between individuals) pharmacokinetics	Must know long t½ and oral bioavailability to pass
THIRD QUESTION (if needed)	**What advantages and disadvantages might a drug like buprenorphine have in the treatment of heroin addiction, as compared to methadone?**	
POINTS REQUIRED	1. Buprenorphine is a partial agonist at the μ receptor, and has a long duration of action due to slow dissociation from μ receptors. Said to be as effective as methadone in the detoxification and maintenance treatment of heroin addiction	Must describe what it does and that it is relatively safe to pass
	2. Lower risk of overdose fatalities compared to methadone due to its partial agonist action	
	3. Slower receptor dissociation renders its effect resistant to naloxone reversal and preventions action of other narcotic analgesics (if needed),	

Oxycodone 2016-2-A

Stem: Moving onto Pharmacology. Oxycodone is prescribed for her arm pain.			
Question 5 Oxycodone-pharmacokinetics and pharmacodynamics **Subject:** Pharmacology LOA: 1	1) Describe the pharmacokinetics of oxycodone	**Good oral absorption** High Vd Low first pass metabolism (cf morphine) **Duration of action 3-4 hours, longer if controlled release formulation** Hepatic metabolism by P450 Metabolites excreted by kidneys	Bold + 1
	2) How does oxycodone produce its analgesic effects	Opioid agonist that acts mainly on **mu receptors** in brain and spinal cord, but also outside CNS	Bold
	3)What strategies may be used when prescribing oxycodone to reduce the development of dependence	Establish goals at start of Rx Combine with non-opioid analgesics Smaller doses at longer intervals Use of controlled release preparations Frequent evaluation of ongoing requirements	3/5

Oxycodone 2014-2-D

Stem: A patient presents with a penetrating eye injury. He has been given oxycodone. Commencing with pharmacology			
TOPIC	QUESTIONS	KNOWLEDGE **(essential in bold)**	NOTES
Question 1 Oxycodone (p 558) **Subject**: Pharm LOA: 1-2	Describe the pharmacokinetics of oxycodone? Prompt: Describe the pharmacokinetics of opiates.	**Oral commonly** Good oral absorption High Vd **Low first pass metabolism CW others** 10 morphine = 4.5mg oxycodone duration 3-4h, longer if CR formulation. Hepatic met	Bold plus one more N+V a particular concern in context of penetrating eye injury
	What adverse effects might you anticipate?	Sedation/Respiratory depression/N+V/hypotension/dysphoria/biliary colic/pruritis/caution in renal failure	3 to pass
	When prescribing oxycodone what prescribing strategies may help in reducing the development of, dependence.	**Smaller doses at longer intervals**/establish goals at start of Rx/**limit doses/use of other analgesics**/frequent evaluation of ongoing need/**use of modified CR formulations**	2 to pass

Paracetamol 2017-2-D

Stem: Moving onto Pharmacology. She has taken excess amounts of Paracetamol for her pain.			
Question 3 Paracetamol **Subject:** Pharm LOA: 1	(a) Describe the pharmacokinetics of oral paracetamol. *Prompt: How is it metabolised?*	Absorption: Well absorbed from the GIT. Peak plasma levels 30-60 minutes. It is slightly protein bound. Distribution: T ½ of 2-3 hours. This is increased in liver disease to >6 hours Metabolism: **Hepatic: >95% undergoes glucuronidation and sulfation.** **5% undergoes metabolism via CYP 450 mechanisms** (Phase 1 reaction – hydroxylation) to form NAPQI. NAPQI is toxic, but usually detoxified by glutathione.	Bold to pass
	(b) What is the toxic dose of paracetamol?	150 - 200mg/kg in adult	
	(c) How does paracetamol cause toxicity?	In ODs → glucuronidation and sulfation pathways are saturated and paracetamol is broken down by a Phase 1 reaction. More NAPQI is formed → this consumes glutathione (GSH). Once GSH is depleted, NAPQI then becomes hepatotoxic.	Concept to pass

Paracetamol 2016-1-C

Stem: Moving onto Pharmacology. He is given paracetamol for his fever.			
Question 5 Paracetamol **Subject:** Pharm LOA: 1	1. Describe the pharmacokinetics of paracetamol.	Rapid absorption. Bioavailability 70-90%. Peak concentration after 30-60 mins. Slight ppb. Partial metabolism by hepatic MEs to paracetamol glucuronide and sulphate (90%). First order kinetics. T1/2 2-3 hours. <5% excreted unchanged.	4 points to pass (out of total 8)
	2. What is its mechanism of action?	Selective **COX-2 inhibitor**.	bold to pass
	3. What is the mechanism of paracetamol toxicity?	Zero order kinetics. paracetamol is conjugated with glucuronide and sulfate (by transferase enzymes) - this **pathway becomes saturated** in OD, allowing increasing paracetamol to be metabolized by the smaller CYP 2E1 pathway to NAPQI. NAPQI is detoxified by **glutathione** which becomes depleted resulting in high levels of **toxic metabolite (NAPQI).**	bold & concept to pass
	4. *[If time only]* What are the clinical manifestations of toxicity?	Nausea, vomiting, abdominal pain, liver failure, renal failure (tubular necrosis), HAGMA, massive doses - coma.	4 to pass

Paracetamol 2012-1

	the pharmacological action of the drug?	of the administered drug?	
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

Paracetamol 2010-1

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)

Paracetamol 2007-2

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

Paracetamol 2005-2

TOPIC: Paracetamol _____ **NUMBER: 4** _____

OPENING QUESTION	**Tell me about the pharmacokinetics of paracetamol**	**COMMENTS**
POINTS REQUIRED	1. **Well absorbed** orally with peak concentrations 30-60 mins	1-3 to pass
	2 **Hepatic metabolism** Conjugated to sulphate and glucuronide which are inactive.	
	3 **Renal excretion** of conjugate. < 5% unchanged	
	4 **Minor metabolite is toxic**. N-acetyl-p-bemzoquinone. Detoxified by glutathione.	
	5.Elimination t ½ 2-3 hrs	
	6. No plasma binding. VD 1L/kg (approx = TBW)	
	7. Activation of P450 system increases metabolism and toxic metabolite. Serum 150-200 mg/l normally 100 mg/L if enhanced	
PROMPTS		
SECOND QUESTION (if needed)	**How does n-acetylcysteine work in treatment of paracetamol overdose?**	
POINTS REQUIRED	1.serves as substrate for toxic metabolite to act on	1 to pass
	2 Glutathione substitute. SH donor	
	3 Early	
PROMPTS		

Paracetamol 2004-2

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	

Salicylate toxicity 2006-1

Salicylate toxicity	Outline the clinical features of salicylate toxicity? *Prompt if required* *What are the acid base disturbances in salicylate toxicity?* Describe the enhanced elimination strategies employed in managing a patient with salicylate overdose?	**Salicylism: hearing/tinnitus** **Any CNS:** coma **GIT disturbance** Hyperthermia **Respiratory Alkalosis** **Metabolic Acidosis** **pH Manipulation /urinary alkalinisation** Forced Diuresis **Dialysis** *Prompt for both*	Hypoglycaemia Coagulopathy Renal failure Uncoupling Oxidative Phosphorylation Dialysis procedures 1. Peritoneal dialysis 2. Hemodialysis 3. Hemoperfusion