Clotting VIVAs (Pharmacology)

shakEM

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2015.1D

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.

2014.2B

Question 3 Heparin (pp 604-607) **Subject:** Pharm LOA: 1	1. How does heparin act?	Heparin binds endogenous **antithrombin and enhances its activity. Antithrombin inhibits factors IIa, IXa and Xa** by complexing with them and inducing a conformational change.	Bold to pass
	2. How may heparin be administered?	**IV vs SC.** Continuously (following bolus) vs intermittent. Therapeutic vs prophylactically	Bold to pass
	3. What are the potential adverse effects?	**Bleeding,** allergy, alopecia, osteoporosis, **HIT,** mineralocorticoid deficiency	Bold + 1 to pass
	4. What are the advantages of low molecular weight heparins compared to unfractionated heparin?	Have equal efficacy, increased SC bioavailability, require less frequent dosing, and less monitoring. Shorter chain heparin with less effect on thrombin (IIa).	Demonstrates understanding

2014.1C

Question 2 Vitamin K **Subject:** Pharm	What methods are available to reverse warfarin induced anti-coagulation? How does vitamin K reverse warfarin	**Cease warfarin** **Vit K – oral or IV 1-10mg** **+/- FFP or prothrombinex**	2/3 bold to pass, must include vitamin K.
LOA: 2	effect?	Pharmacodynamic interaction with warfarin to reduce INR ie **reverses the effect of warfarin Re-establishes normal activity of the clotting factors. Vit K dependant clotting factors: II, VII, IX,X**	Bold to pass
	How long does it take for vitamin K to work?	**6 - 24 Hours**	>6 hrs

2012.1.3

Question 4 LOA: 1 **WARFARIN**	What is the mechanism of action of warfarin?	Warfarin **inhibits reduction of inactive Vit K** epoxide (KO) to active hydroquinone (KH_2) form. Blocks γ-carboxylation of glutamate residues in **prothrombin (Factor II) and factors VII, IX and X** ,as well as endogenous anticoagulant protein C and S.	Need to know role of vitamin k
	Why is there a delay in the onset of action of warfarin?	8-12 hr delay due to partially inhibited synthesis and unaltered degradation of 4 vit k dependent clotting factors and depends on **degradation ½ life** in circulation eg factor VII- 6 hrs, IX 24-hrs, X - 40 hrs and II- 60 hrs)	Need to have some idea of delay in onset
	What pharmacological agents are used in the reversal of warfarin?	Vitamin K. FFP. Prothrombin Complex. Recombinant FVIIa	
	Optional: Describe the mechanisms of drug interactions with warfarin	Pharmacokinetic: Enzyme induction + inhibition. Altered protein binding Pharmacodymanic: Synergism. Competitive antagonism (Vitamin K)	3 required

2012.2.2

Question 4 Warfarin Interactions LOA: 1	Describe the mechanisms by which drugs interact with Warfarin. *Prompts* *Please describe pharmacokinetic interactions* *Please describe pharmacodynamic interactions*	**PK - Enz inhibition** (majority), **Enz induction**, altered, plasma protein binding, altered abs **PD** – Synergism (**impaired haemostasis)** Competitive antagonism (**clotting factor synthesis/concentration**)	Must get one example of PK and PD
	Give some examples of drugs that increase the INR.	↑ **INR**: aspirin, heparin, corticosteroids metronidazole, fluconazole, trimethoprim-sulfamethoxazole, third generation cephalosporins, macrolides, amiodarone, SSRIs, tramadol	Must give at least 1 example of each
	Give some examples of drugs that decrease the INR.	↓ **INR:** Vit K, diuretics, barbiturates, phenytoin, carbamazepine, rifampicin, diclox, azathioprim	

2012.2.3

Question 4 Tisssue Plasminogen Activator LOA 1	Describe the mechanism of action of tissue plasminogen activator (tPA)?	Activates **plasminogen to form plasmin**, resulting in fibrin digestion. Preferentially activates plasminogen bound to fibrin by several hundred fold therefore is considered **clot specific.** Short half life therefore heparin is essential adjunct. Naturally occurring.	Bold
	What are the clinical uses of tPA? *Prompt: Are there are any other time-critical indications?*	**AMI, unstable PE, acute ischaemic stroke**, severe DVT, intra arterial peripheral limbs	First 3 to pass
	What are the complications of tPA?	**Haemorrhage.** Physiological hemostatic thrombi at site of vascular injury eg GIH, or systemic lytic state resulting from formation of plasmin, producing fibrinogenolysis and destruction of other coagulation factors esp V and VIII.	Must give more than one site.

2012.2.4

Question 5 Heparin LOA: 1	Describe the mechanism of action of heparin?	Binds to endothelial cell surfaces and plasma proteins and its activity depends on antithrombin Heparin binds to antithrombin, causes a conformational change in the inhibitor, exposing its active site for more rapid interaction with proteases. Heparin acts as a co factor for the antithrombin-proteases reaction Antithrombin inhibits proteases espec thrombin 2a, 9a, 10a by forming stable complexes with them and the presence of heparin accelerates this reaction 1000x The binding of AT III and unfractionated heparin ↑ degradation of both factor Xa and thrombin	**Binds to AT III**
	How is heparin reversed? *Prompt: is there a specific antidote?*	Stop the drug Administer antagonist **protamine** (100 units heparin-1mg protamine) which binds heparin to form a complex devoid of anticoag activity Excess protamine anticoag effect	**Bold**
	What are the potential adverse effects of heparin? Prompt: Are you aware of any less common but serious idiosyncratic effects?	**Bleeding** (elderly women, renal failure more prone) **TCP** (1-4%), rare pregnancy, lower rates in paediatrics. Mortality relates to thrombosis Allergy ↑ hair loss Reversible alopecia Accelerates the clearing of post prandial lipaemia by causing release of lipoprotein lipase from tissues Long term: osteoporosis, spontaneous fracture, mineralocorticoid deficiency	**Bold**

2011.1.1

Warfarin-pharmacokinetics and drug interactions	Describe the mechanisms for drug interactions with warfarin and give examples. *Prompts:* *Please describe a pharmacokinetic interaction with warfarin* *Please describe a pharmacodynamic interaction* *What drugs could increase the INR* *What drugs could decrease the INR*	**PK - enz inhibition** (majority), **Enz induction**, altered plasma protein binding, altered abs (cholestyramine p 157) **PD –** bioavailability of Vit K, **influencing Vit K dependant clotting factors,** drugs affecting haemostasis (**1 eg**) ↑ INR: Amiodarone, aspirin, azitrhomycin, cephalosporins, cimetidine, erythromycin, phenytoin, quinidine, SSRI, valproate, metronidazole, hyperthyroid ↓ INR: AZT, barbs, carbamazepine, haloperidol, rifampicin, Vit K, St Johns Wort p159, hypothyroid, cabbage	Must get bold items Must give at least 1 example of each

2010.1.1

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

2009.2.1

Question 4: **Warfarin**	(a) What is the mechanism of action of warfarin?	• Blocks synthesis of Clotting Factors II, VII, IX, X and Anticoagulant proteins C and S • Coupled to Deactivation of Vitamin K	Blocks factors II, VII, IX, X

	(b) What drug interactions with warfarin prolong the INR (prompt for mechanism)?	• Pharmacokinetic: (↑ INR)
		  • Inhibit transformation of Warfarin: S-Metronidazole, Fluconazole, Bactrim; R & S-Amiodarone, Disulfiram, Cimetidine
		  • Displace albumin bound warfarin: phenylbutazone, sulphinpyrazone
		• Pharmacodynamic: (↑ INR)
		  • Aspirin – affects platelet function
		  • 3rd generation Cephalosporins – reduce gut flora producing Vit K
		  • Heparin – directly prolongs INR
			2 examples

	(c) How is the action of Warfarin reversed?	• Vitamin K: FFP:Prothrombin complex – Prothrombin X: Recombinant Factor VIIa	2 of 4

2009.2.2

Question 4: **TPA**	(a) How does TPA work?	• Fibrinolytic. Binds to fibrin in a thrombus and converts entrapped inactive plasminogen to active plasmin to initiate local fibrinolysis	Definition
	(b) What are the indications for TPA use?	• STEMI • PE with haemodynamic instability • Acute Ischaemic Stroke: • Severe DVT	AMI, stroke and 1 other

2008.1.1

LMWH	What are the pharmacodynamic differences between low molecular weight and unfractionated heparin? What are the advantages of low molecular weight heparin over unfractionated heparin?	Enoxaparin predominantly binds and inhibits factor Xa function, UFH binds to AT that inhibits factors II, IX, X Single daily or divided subcutaneous doses – facilitates patient mobility and OPD management. Routine monitoring not required (not mentioned in book) Reduced bleeding risk. Lower incidence of HITP. Improved efficacy over unfractionated heparin in ACS. Increased bioavailability (Pass – dosage differences and bleeding risk as well as factors II and IX less inhibited by LMWH (or at least that APTT is not accurate measurement of anticoagulation)	

Older

FIRST QUESTION	How does unfractionated heparin work?	
	Heterogenous mixture of sulfated mucopolysaccharides which binds to endothelial cell surfaces **Binds to ATIII** – conformational change so active site exposed for more active interaction with proteases to inhibit them from clotting (VIIa, IX a, Xa, II a) Heparin speeds up process 1000x. Heparin not consumed in process	
SECOND QUESTION	How does the mechanism of action of LMW heparins differ?	
	Inhibit activated factor X but less effect on AT and coagulation Increased bioabilability from SQ site of injection Need less frequent dosing (1-2/day) Don't need to follow APTT	
THIRD QUESTION	What is the adverse effects?	
	Bleeding – incr. in elderly, renal failure Transient **thrombocytopenia** 25% patients, severe in 5% Heparin induced thromocytopenia – heparin induced Ab against heparin platelet factor 4 complex Long term – osteoporosis, spontaneous fractures, mineralocorticoid deficiency	
FOURTH QUESTION	What is the clinical advantage of LMW over unfractionated heparin	BONUS
	Ease of administration – IV/SQ; timing; place question	

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.	

		Common or Common to group **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 Some NSAID,s 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	

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		

4. Anti-platelet agents	1.What is the mechanism of aspirin's antiplatelet action? 2. What other types of anti-platelet agents are there? 3. What are the clinical indications for anti-platelet agents?	Irreversible inhibition of COX Inhibits synthesis of thromboxane A2 Inhibitors of ADP pathway 2b,3a blockers beta blockers Other NSAIDs IHD TIA/CVA Pregnancy: prophylaxis pre-eclampsia Post acute coronary intervention	Needs Irreversible inhibition of COX The first two, others bonus. Can give name or example 3 out of 4	

Antiplatelet agents	Describe the mechanism of action of clopidogrel. How does it differ from aspirin? What other types of anti platelet agents are there?	**Irreversibly blocks the ADP receptor on platelets to inhibit platelet aggregation.** **Asprin inhibits the synthesis of Thromboxane A2** within platelets by the **irreversible acetylation of cyclooxygenase. (1 of 2)** **Phosphodiesterase inhibitors (dypridamole)** **Glycoprotein IIb/IIIa inhibitors (abciximab) (1 of 2)**	Thienopyridine derivative. Unlike asprin has no effect on PG metabolism

4. Clopidogrel	1. What is the mechanism of action of clopidogrel? 2. How long is this effect 3. What are the indications for clopidogrel (1/2 for pass)	Irreversible blockade of platelet ADP receptors, leading to inhibition of platelet activity Note there is no anti-prostaglandin effect cf aspirin 7-10 days IHD – pre/post stent, stroke prevention	

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

Vit K	What are the preferred administration routes for Vitamin K? What are the clinical indications for prescribing Vitamin K?	**Oral, , im iv** SC erratic **Reversal of oral anticoagulant effect** **Management of warfarin toxicity** or superwarfarin toxicity (brodifacoum) **Vit K defic** Prevention of haemorrhagic disease of the newborn Treatment of haemorrhagic disease of the newborn	ORAL DOSE - Absorption is inconsistent Rapid intravenous infusion may produce flushing, cyanosis, dizziness, hypotension, and bronchoconstriction. ORAL VITAMIN may be indicated in small ingestions or when the amount is uncertain, but presumed to be small. INTRAVENOUS VITAMIN K INDICATIONS - Intravenous phytonadione is preferable in SEVERE cases where rapid correction is required. Adults: A minimum of 10 mg IV diluted in saline or glucose at a rate not exceeding 5 percent of the total dose per minute. In maximally anticoagulated individuals, repeat doses at 6-8 hour intervals

Warfarin interactions	Describe the pharmacokinetic mechanisms for drug interaction with oral anticoagulants? Describe a pharmacodynamic interaction with warfarin?	**Enzyme induction or enzyme inhibition** **-reduced plasma protein binding (all 3)** -competitive antagonism Vit K Pharmacodynamic: aspirin, heparin, 3rd gen cephalosporin -altered physiologic control loop - hereditary resistance -clotting factor conc-spironolactone	Pharmacokinetic: amiodarone, metronidazole, trimethoprim **At least 2 examples** *Prompt "what happens to a patient on warfarin who is given Vit K"* *"why does the INR alter?"*
heparins	Describe the mechanism of action of heparin?	**Binds to Antithrombin III** and accelerates its inhibition of clotting factor proteases (1000 fold).	Heparin binds to endothelial cell surfaces. About 1/3 of heparin molecules have a unique polysaccharide needed for high affinity binding to AT III, which then causes a conformational change to expose the active site of AT III for more rapid interaction with the proteases (activated clotting factors). Heparin catalyzes the AT III-protease reaction without being consumed and can move on to bind more AT III.
	How can heparin be reversed? *Prompt* *What dose of protamine should be used?*	• stop the drug • **Administration of antagonist – protamine** sulphate For every 100 Units Heparin need 1mg Protamine, but excess protamine must be avoided as can have anticoag effect	Protamine binds with heparin to form stable complex devoid of anticoagulant activity
	What are the potential adverse effects of heparin? *Prompt* *"what are the different types of TCP seen in patients on heparin?*	• Bleeding • **Thrombocytopaenia**	Elderly and pts with renal impairment more prone; contraindicated in pts with bleeding disorders, GIT ulcers, infective endocarditis and active TB, etc Transient in 25% patients ?due to heparin induced aggregation - benign
			5% severe due to antibody-mediated cause – antibody generated against heparin-platelet factor 4 complex causing aggregation and paradoxical thromboembolism; may be aggravated by warfarin

1.4 tPA	How does tPA work. How does tPA differ from streptokinase?	**tPA activates plasminogen already bound to fibrin, to form plasmin.** Plasmin degrades fibrin to fibrin split products. This *theoretically* confines fibrinolysis to formed thrombus. **Short half life** means **heparin** is an essential adjunct. **tPA** is a **naturally occurring human enzyme. Streptokinase** is not an enzyme itself- it is a **bacterial product** that combines with plasminogen to form an enzymatic complex catalyses conversion of plasminogen to plasmin. **Long half life** means that heparin is not required (and may increase bleeding risk). **Prior streptococcal infection** may result in antibodies that cause fever, allergic reactions and therapeutic resistance. **Prompts (if needed):** - *"compare and contrast the methods of administration and the adjunctive use of heparin"* - *When might streptokinase be ineffective?"*	/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	/2
	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	