Endocrine and Electrolyte VIVAs (Pharmacology)

shakEM

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2015.1C

Question 4 Sulfonyl Ureas **Subject:** Pharm LOA: 1	1. What class of drug is gliclazide? 2. Describe the mechanism of action of sulfonylureas. 3. What are the pharmacokinetic properties of gliclazide? 4. What are potential adverse effects of gliclazide?	**1. Sulphonylurea** **2. Stimulates insulin secretion from functional pancreatic beta cells** • Binding of sulphonylurea to receptor inhibits potassium efflux causing extracellular depolarisation • Results in opening of voltage gated calcium channels • Calcium influx causes release of preformed insulin 3. Administered orally – good oral bioavailability (80%) Protein bound – volume of distribution ~ 20L **Hepatic metabolism** to inactive metabolites **Half life approx. 12 hours** Predominantly renally excreted (80%) **4. Hypoglycaemia** **GI upset** – nausea, vomiting, abdominal pain, diarrhoea Rash/pruritis	Bold to pass Bold Bold Hypoglycaemia plus one

2014.2A

Question 4 Metformin (p 757) **Subject:** Pharm LOA: 1	1. Describe the pharmacokinetics of metformin 2. Outline some common side effects of metformin 3. Contrast the mechanism of action of metformin (biguanide) and glipizide (sulfonylurea).	Well absorbed, not protein bound, not metabolised, elimination half-life 1.5 to 3 hours **Excreted by kidney as unchanged compound.** **GI most common (20%) – limits compliance with this drug.** HAGMA **(lactic acidosis)** esp in patients with coexistent renal disease, EtOH, chronic cardiopulmonary disease. Glipizide – **Increases insulin release from pancreas** (patients more prone to hypoglycaemia with glipizide compared with metformin) Decreases serum glucagon levels Metformin Mechanism unclear but: May reduce hepatic gluconeogenesis. **Not dependent on functioning pancreatic B cells – so doesn't influence insulin release from pancreas** May directly simulate glycolysis in tissues with increased glucose removal from blood Decreases glucose absorption in the gut	Bold and one other to pass. Bold to pass. Bold to pass.

2014.1B

Question 3 Corticosteroids **Subject:** Pharm LOA: 1	Describe the mechanism of action of corticosteroids at a cellular level?	• Most of known effects via widely distributed **glucocorticoid receptors** • Present in blood in bound form on Corticosteroid Binding Globulin (CBG) • Enters cell as free molecule • Intracellular receptor bound to stabilizing proteins (most important heat shock protein 90, Hsp90) • Complex binds molecule of cortisol then actively transported into nucleus where binds to **Glucocorticoid Receptor Elements (GRE)** on the gene • Interacts with DNA and nuclear proteins regulating transcription. Resulting mRNA exported to cytoplasm for **protein production** for final hormone response	Bold to pass
	How can corticosteroids be classified? Prompt: How do they differ in their action?	1. length of action (hydrocortisone short to medium-acting, dexamethasone or betamethasone long-acting) 2. **anti-inflammatory activity** (potency: hydrocortisone 1, prednisolone 5, dexamethasone 30) 3. **mineralocorticoid activity** ie., salt retaining (fludrocortisones 250 times that of hydrocortisone) 4. topical vs non topical	bold
	What are the side effects of corticosteroid use? Prompt: what about long term effects?	- Short term: (<2 weeks): insomnia, behaviour changes, acute peptic ulcer, acute pancreatitis, hyperglycaemia - Long term: - Cushing's Syndrome (moon facies, fat redistribution, fine hair growth, acne) secondary to hormonal actions. (Rate of development function of dose and genetic background) - hyperglycaemia, diabetes - myopathy - osteoporosis, aseptic necrosis - psychiatric (hypomania, acute psychosis, depression) - Na,fluid retention, K+ loss - **adrenal suppression** / addisonian crisis - poor wound healing **- immunosuppressant**	Bold and 4 others

2014.1C

Question 2 Magnesium **Subject:** Pharm LOA: 1	2.1 What are the indications of its use in pregnancy? 2.2 What are the other uses of magnesium in Emergency Medicine? 2.3 What are the toxic effect of magnesium?	2.1 It is indicated **in pre-eclampsia and eclampsia.** for the prevention and treatment of **life threatening seizures.** 2.2 It has an **anti-convulsant effect,** possible **antiarrhythmic effect, bronchodilator effect.** (influence Na+ /K+ -ATPase, Na channels, certain K and Ca channels). 2.3 Hypermagnesaemia include nausea & vomiting, flushing, hypotension, muscle weakness, muscle paralysis, blur or double vision, CNS depression or loss of reflexes, respiratory depression, renal failure, cardiac arrhythmia.	Bold to pass 2/3 bold to pass 3 to pass

2014.1C

Question 2 Insulins (Katzung 12th ed pp 747-753) **Subject:** Pharm LOA: 1	What pharmacological methods are used to optimise blood sugar control when administering insulin? Prompt: what are the different types of insulin?	1. **Titration of dose to BSL** 2. **Pharmacological manipulation of human insulin molecule**: rapid-acting (aa reversal/substitution reducing aggregation properties), intermediate acting (insulin/protamine complexes), long acting (aa substitutions, molecular attachments) 3. Mixing of insulin preparations 4. Continuous subcutaneous insulin infusion devices	Bold to pass

2012.1.2

Question 4 LOA: 1 **INSULIN**	Describe the different types of insulin used in the routine management of Type I Diabetes. *Prompt: Please describe in terms of duration of action*	**Rapid and short acting** Clear soln, neutral pH, contain Zn rapid onset, short duration e.g. insulin neutral, insulin lispro, insulin glulusine **Intermediate acting** Turbid soln, neutral pH, protamine in phosphate buffer (NPH) to prolong action e.g. insulin isophane, insulin aspart protamine **Long acting** Clear solution, soluble Slow onset, prolonged action Daily admin mimics basal insulin secretion e.g. insulin glargine, insuline detemir	Pass criteria: Identify existence of rapid, intermediate and long-acting insulin Aware that combination of therapies required to cover both basal requirements and post-prandial periods
	How are these properties used to achieve optimum glycaemic control?	Tight glycaemic control is achieved by a combination of insulins with different durations of action with an aim of replacing the basal insulin requirements (50%) and meal requirements (50%). This is done with **combinations of insulins with different duration of actions**	
	What type of insulin is used for intravenous infusion and why?	Short-acting regular soluble insulin as it immediately dissociates on dilution and so is able to more precisely delivered.	
	Optional: Describe the principles of operation of a subcutaneous insulin infusion device. PROMPT: Insulin pump.	External open-loop pump for insulin delivery. Delivers individualised basal and bolus insulin replacement doses based on blood glucose monitoring. Programmed by user. Consists of insulin reservoir, program chip, keypad and display screen attached to subcutaneously inserted infusion set.	

2012.2.1

			poor renal function?
Question 2 Oral hypoglycaemics LOA: 1	Describe the pharmacokinetics of metformin?	Well absorbed, not protein bound, not metabolised, elimination t1/2: 1.5-3 hours, **excreted by kidney** as unchanged compound	Bold
	What are the side effects of metformin?	Gastrointestinal most common 20%, decreased absorption Vit B12, **lactic acidosis** esp with renal disease, ETOH, chronic cardiopulmonary disease	Bold
	With regard to sulphonylureas, what is	**Increase insulin release from the pancreas** bind	Patients more prone to hypo
	the mechanism of action of glipizide? (prompt: it's a sulphonylurea)	to receptor associated with ATP sensitive K channel, inhibits efflux of K ions, results in depolarization and opens ca channel, influx of Ca causes release of preformed insulin Reduction of serum glucagon levels Closure of potassium channels in extrapancreatic tissues	than with biguanides eg metformin

2012.2.1

Question 4 Calcium	Can you give me an example of a preparation of calcium that is taken orally?	**Calcium Carbonate** or Ca -acetate, citrate, glubionate, gluconate, lactate or phosphate	Need to name 1
LOA: 1	What are the possible uses of oral calcium preparations?	i) Treatment of **hypocalcaemia** (eg. in patients with hypoparathyroidism, vit D deficiency, chronic renal disease or malabsorption). ii) As an antacid	hypocalcaemia.
	What are the potential adverse effects of giving calcium intravenously?	Irritation of the veins. Cardiac arrhythmias with rapid administration. Hypercalcaemia.	phlebitis

2011.2.3

Question 5 Adrenocorticoids (Hydrocortisone)	a) What are the effects of hydrocortisone? (Prompt: *Describe the anti-inflammatory and immunosuppressant effects of hydrocortisone)* b) What are the effects of chronic steroid use?	a) Mediated by glucocorticoid receptors Physiologic + permissive effects Metabolic effects Catabolic and anti-anabolic effects Anti-inflammatory + immunosuppressive effects Other effects: CNS, pituitary axis, psychiatric, renal, neonatal lung Effect concentration, distribution + **function of peripheral leukocytes** **Suppress inflammatory mediators** (cytokines + chemokines, as well as PGs + leukotrienes) Inhibit tissue macrophages + APCs Suppress mast cell degranulation Reduce antibody production (in large doses) **c) Cushings Syndrome** Metabolic effects (moon face, fat redistribution, striae, weight gain, myopathy, muscle wasting, thin skin, bruising, hyperglycaemia, osteoporosis, diabetes, aseptic necrosis, wound healing impaired Other effects (peptic ulcers, psychosis, depression, cataracts, glaucoma, salt retention, hypertension) **Adrenal suppression** (> 2 weeks dosage)	Bolded + one other Bolded + 3 others

2009.2.2

Question 2: **Classification of drugs used in diabetes mellitus**	(a) Outline the groups of drugs that are used to treat hyperglycaemia in diabetes mellitus.	• **Insulin** • **Sulfonylureas -** • **Biguanides** • Meglitinides • D- phenylalanine derivatives • Thiazolidinediones • Alpha-glucosidase inhibitors	Must get 3 bolded groups to pass.
	(b) Contrast the mechanism of action of sulfonylureas and biguanides.	Sulfonylurea: • **Increase insulin release from pancreas** • Reduction of serum glucagon levels • Closure of potassium channels in extrapancreatic tissues Biguanide: • **Action does not depend on functioning pancreatic B cells** • May directly stimulate glycolysis in tissues with increased glucose removal from blood; • May reduce hepatic gluconeogenesis; • May slow of absorption of glucose from the GI tract; • May reduce glucagon levels	Bold to pass

2008.2.1

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

2008.2.2

Question 5: Thioamides	1. How does carbimazole act in thyroid disease?	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	Bold to pass
	2. What are the major side effects of carbimazole?	Rash maculopapular, pruritus – common; **B one marrow suppression**: neutropenia, agranulocytosis (reversible). Others – urticaria, arthralgia, lupus reaction, vasculitis, jaundice/hepatitis; nausea and GI, occur early	1 side effect
	3. How does carbimazole differ from propylthiouracil?	**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)	Bonus marks

Older

FIRST QUESTION	What are the different types of oral antidiabetic agents ?	
	a. Insulin secretagogues (**sulfonylureas,** meglitinides) **b. Biguanides** c. Thiazolidinediones – enhance target tissue insulin sensitivity d. Alpha-glucosidase inhibitors – competitive inhibitors of intestinal alpha glucosidases – defers digestion to distal small intestine	
SECOND QUESTION	What is the mechanism of action of the sulfonylureas	
	- increase insulin release from pancreas - reduce serum glucagons levels - extrapancreatic effect to potentiate action of insulin on target cells (last 2 ?clin.sig.)	
THIRD QUESTION	How do the biguanides differ from the sulfonylurease in their action	
	Not need functioning pancreatic B cells - direct simulation of glycolysis in tissue - reduce hepatic gluconeogensis - slowing glc.absorption from GI tract - reduction of plasma glucagons levels	
FOURTH QUESTION	What are the clinical advantages of the different oral antidiabetic agents?	
	a. Biguanides = **Refractory obesity** where insulin resistance b. Combination with sulfonylureas in Type II Diabetes c. Newer sulfonylureas are liver metabolized so can be used in renal failure	

Glucagon pp730-2	Regarding glucagon outline its pharmacodynamic effects and relate these to its clinical use.	• Glycogenolysis and gluconeogenesis thus increasing serum glucose –treatment of hypoglycaemia • Positive ionotropic and chronotropic effect on the heart via glucagon receptors and cAMP – treatment of B Blocker OD. • Relaxation of intestinal smooth muscle – treatment of food bolus obstruction or to aid radiology of the bowel	To pass: must get hypoglycaemia and one other, others bonus	

B receptor agonists	1. Regarding B agonists, by what cellular mechanism do they exert their effects?	Bind to specific **receptor.** **G-protein activation.** Stimulate adenyl cyclase. **Increased cyclic AMP.** **Increased free intracellular Ca.** Activate protein kinase.	**Bold items required to pass.**	
	2. Compare the cardiovascular of adrenaline and dobutamine.	**Adrenaline has B1, B2 and alpha effects.** Increased **inotrope and chronotrope.** Peripheral **vasoconstriction in most vascular beds.** Vasodilatation in skeletal muscle beds (B2). May reduce TSVR. **Dobutamine is a selective B1 agonist.** **Increases cardiac output** with less reflex tachycardia as it has fewer B2 effects. Comes as racemic mixture of +ve and –ve isomers. One isomer has B agonist and alpha antagonist effects; the other has alpha agonist effects.	**Bold items required to pass.**	

Oral hypoglycaemic agents	1. Regarding sulphonylureas and bigaunides, compare their mechanisms of action.	**Sulphonylureas increase insulin release.** Act via a specific receptor which causes an increase in intracellular Ca, which triggers insulin release. There are also receptors in cells on binding proteins in secretory granules, which may cause a direct action on exocytosis of insulin. Other peripheral effects may be to reduce serum glucagon and potentiate insulin effects on cells. **Biguanides** are 'euglycaemic agents". They **do not require functional islet cells to reduce blood sugar.** Their possible actions are to directly stimulate glycolysis in tissues and blood; reduce hepatic gluconeogenesis; reduce GIT absorption; reduce plasma glucagon.	**Bold items required to pass with some additional explanation.**	
	2. How do the major side effects of the two groups of drugs differ?	**Biguanides can cause lactic acidosis.** They reduce gluconeogenesis and reduce lactic acid uptake in the liver. More likely in patients with renal disease, alcoholism, liver disease and chronic tissue hypoxia. **Sulphonylureas more commonly cause hypoglycaemia.** More likely in the elderly and with drugs with long t ½ e.g. chlorpropamide.	**Bold items required to pass with some additional explanation.**	

5. Hydro-cortisone	1. Regarding hydrocortisone, what are its pharmacodynamics? Describe the anti-inflammatory and immunosuppressant effects of hydrocortisone?	• Anti-inflammatory • Immunosuppressive • Catabolic effects • Permissive effects • Metabolic effects • Other: endo, psych Altered leucocyte concentration, distribution and function Inhibit macrophages and antigen presenting cells Reduce interleukins and other mediators Phospholipase A2 and COX 2 Decrease histamine release by mast cells, etc Reduce Ab production	Pass = First 2 plus 1. Pass = two	
	3.What are the effects of chronic steroid use?	Cushings	Several features	

Insulin	Describe the action of insulin on the liver What are the complications of insulin therapy ?	Anabolic, anti catabolic 2 of immune,hypoglycaemia, lipodystrophy, immune resistance		

3. Dexamethasone	**1.What are the pharmacological differences between dexamethasone and hydrocortisone?** **2.In what situations could you use dexamethasone** (3 EXAMPLES FOR PASS)	**1. 30x greater anti-inflammatory potency** **2. Longer duration of action** **3. No salt retaining activity** **1. Diagnosis – dexa suppression test** **2. Anti inflammatory effect (see table 39-2 p651)** **3. Croup**	

1.5 Erythropoeitin	What is erythropoietin What are its clinical applications? What toxic effects may occur?	- **Glycoprotein produced by kidney** - **Stimulates red cell precursors to proliferate and differentiate.** Also releases reticulocytes from marrow - Main use is for the **anaemia of chronic renal failure**, where erythropoietin production in impaired - Helps some **marrow failure** states (aplastic anaemia, myeloproliferative/myelodysplastic disorders, multiple myeloma, AIDS and cancer) **(must get one of three)** - Toxicity mainly related to rapid Hb rise o Hypertension o Thrombosis **(must get one of two)** (Allergic reactions are infrequent and mild)	/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? 2. What are the indications and dosage of colchicine? (either 1 or 2 to pass)	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 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