Primary Cast Episode 23 - Endocrine & GIT Pharmacology

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1. **Thyroid Pharmacology**

   How does carbimazole act in thyroid disease?

   Metabolised to methimazole
   Major action is to block hormone synthesis (T3 and T4)
   Inhibits thyroid peroxidase enzyme which limits the organification of iodine.
   Small action in blocking peripheral deiodination of T3 and T4
   Slow onset as T4 may take weeks to be depleted

   What are the major side effects of carbimazole?

   - Rash - maculopapular
   - Pruritus
     Bone marrow suppression: neutropaenia, agranulocytosis (reversible)
   - Jaundice/hepatitis
   - Nausea and GI effects
   - Arthralgia
   - Vasculitis

   How does carbimazole differ from propylthiouracil?

   - Carbimazole is a prodrug - converted to methimazole in vivo. Methimazole is 10 times more potent than carbimazole.
   - PTU has greater action in inhibiting peripheral deiodination of T4 and T3
   - PTU has a shorter half life 1.5 vs 6 hours. So means PTU given QID and Carbimazole once daily
   - PTU bioavailability 50-80% vs carbimazole 100%
   - PTU excreted in the urine as a glucuronide metabolite in <24 hours, carbimazole takes over 48 hours

2. **Corticosteroids**

   Describe the mechanism of action of corticosteroids as a cellular level

   - Most of known effects are via widely distributed glucocorticoid receptors
   - The drug is present in the blood in bound form on corticosteroid binding globulin
   - Enters the cell as a free molecule
   - The intracellular receptor is bound to stabilising support proteins
   - The complex binds a molecule of cortisol and then is actively transported into the nucleus where it binds to glucocorticoid receptor elements on the gene
   - Interacts with DNA and nuclear proteins that regulate transcription, resulting in mRNA exported to cytoplasm for protein production for the final hormone response

What are the effects of corticosteroids?
This is a question about *pharmacodynamics*

- Cardiac - Permissive effect on catecholamines
- Metabolic - catabolic, anti-anabolic effects
- Anti-inflammatory effects - influences the effect, concentration and distribution of peripheral leukocytes, suppresses inflammatory mediators, inhibits tissue macrophages.
- CNS effects - insomnia

What are the effects of chronic steroid use?

- Cushing's syndrome
- Peptic ulcers
- Cataracts + glaucoma
- Psychosis and/or depression
- Hypertension
- Adrenal suppression with use for > 2 weeks

3. **Diabetes Drugs**

Outline the groups of drugs used to treat diabetes

- Insulin
- Sulfonylureas
- Biguanides
- Meglitinides
- Alpha glucosidase inhibitors

What are the pharmacokinetics of sulfonylureas?
A: Oral administration with 80% bioavailability
D: Protein bound with a volume of distribution of approx 20L
M: Hepatic metabolism to products which are inactive or have very low activity. Variable but moderate half life of 8 - 24 hours
E: Renally excreted

Contrast the mechanism of action of sulfonylureas and biguanides
Sulfonylureas i.e. glipizide

- Increase insulin release from the pancreas (specifically from pancreatic beta cells)
- They bind to a cell surface receptor and cause depolarisation by inhibition of K+ efflux. This leads to release of preformed insulin
- Reduce serum glucagon levels
- Also facilitates closure of potassium channels in extrapancreatic tissues

Biguanides i.e. metformin

- Action does not depend on functioning pancreatic beta cells

- Mechanism is still unclear but evidence that it:
- May directly stimulate glycolysis in tissues with increase glucose removal from blood
- May reduce hepatic gluconeogenesis
- May slow absorption of glucose from the GI tract
- May reduce glucagon levels

Describe the pharmacokinetics of metformin
A: well absorbed
D: Not protein bound
M: Not metabolised
E: Elimination via kidney excretion as an unchanged compound with an elimination half life of 1.5 to 3 hours

What are some of the side effects of metformin?
GI upset most common and often limits compliance with the drug
High anion gap metabolic acidosis - especially in patients with co-existing renal disease, EtOH excess or chronic cardiopulmonary disease

4. **Insulin**

What is the action of insulin?
This is a question about *pharmacodynamics*
Promotes the uptake of glucose from blood into tissues - especially fat, liver cells and skeletal muscle. Promotes glycogen synthesis.

What different formulations of insulin are there?
Rapid and short acting - clear solution, rapid onset, short duration e.g. insulin lispro
Intermediate - turbid solution, protamine buffer to prolong action e.g. protaphane insulin
Long acting - clear solution, slow onset, prolonged action. Daily administration mimics basal insulin secretion. E.g. insulin glargine

How are the different properties of these types of insulin used to optimise glycaemic control?
Combination of insulins with different durations are used to form a basal bolus routine where half is given as long acting and the other half is given in divided doses associated with meals

What type of insulin is used for intravenous infusion and why?
Short acting regular soluble insulin as it immediately dissociates on dilution and is able to be more precisely delivered

Can you provide any other emergency department uses for insulin aside from glucose control?

- Treatment of hyperkalaemia
- Management of toxic overdoses i.e. calcium channel blockers or beta blockers

What are the possible adverse effects of insulin therapy?

- Hypoglycaemia
- Insulin allergy - usually due to non-insulin contaminants
- Immune insulin resistance
- Lipodystrophy at injection sites

5. **Glucagon**

Describe the pharmacologic effects of glucagon

Metabolic

- Binds with receptors on liver cells (G protein linked)
- Promotes catabolism of stored glycogen, raining the blood glucose level
- Has no effect on skeletal muscle
- Causes release of insulin from beta cells

Cardiac Effects

- Potent inotropic and chronotropic effect on the heart via cAMP without requiring functioning beta receptor

Other

- Large doses of glucagon produce relaxation of smooth muscle

What are the indications for using glucagon clinically

- Severe hypoglycaemia
- Can be used as an adjunct in anaphylaxis in patients on beta blockers who fail to respond to adrenaline
- Relaxation of intestine during some radiological procedures
- Diagnosis of endocrine disorders i.e. diabetes, some tumours including pheochromocytoma
- Previously first line for treatment of beta blocker overdose - used to reverse hypotension/bradycardia due to the ability to increase cAMP production in the heart independent of beta-receptor function. Now not really done due to lack of evidence and superiority of high dose euglycemic insulin therapy.
- Previously also used to treat food bolus but not done anymore due to side effects and poor effectiveness

What are the adverse reactions produced by glucagon?

- Relatively free from severe reactions
- Transient dose-dependent nausea and vomiting
- Hyperglycaemia
- Anaphylaxis always possible

6. **Octreotide**

What is the mechanism of action of octreotide?

- Somatostatin analog
- Reduced splanchnic and portal blood flow by poorly understood mechanisms and hence variceal pressures
- Inhibits endocrine and paracrine factor secretion including insulin, glucagon, gastrin, GH and TSH

What are the pharmacokinetics of octreotide?

A: IV, IM, subcut
D:
M: Mostly metabolised by the liver
E: plasma elimination half life is 80 mins, 20% excreted unchanged

What are the adverse effects?

- Anaphylaxis
- Local irritation during injection
- GI symptoms - nausea, vomiting, decreased intestinal motility
- Hypo OR hyperglycaemia - unpredictable
- Cardiac - sinus brady, conduction disturbances

What are some of the clinical uses of octreotide?

- Acute oesophageal variceal bleed - to divert blood from the splanchnic circulation and decrease postal pressure
- Used in sulfonylurea overdose
- Reduce symptoms of hormone secreting tumours e.g. carcinoid syndrome

7. **Terlipressin (not included in previous exams but now clinically used in variceal bleed instead of octreotide so fair game for new questions, also useful in an emergency!)**

What is the mechanism of action of Terlipressin?

Synthetic vasopressin analogue with relative specificity for splanchnic circulation where it causes vasoconstriction of these vessels with a reduction in portal pressure

What are the pharmacokinetics?

A: Given IV, concentration increases proportionally with the dose administered
D: VD of 6.3L
M: Converted to active metabolite lypressin via tissue peptidases. Not affected by liver/kidney disease states. Half life of the active metabolite is 3 hours.
E: Less than 1% of terlipressin or lypressin is excreted unchanged

What is it used for?

Mostly in acute management of variceal bleed to divert blood from splanchnic circulation.

Also used non-emergently in hepatorenal syndrome

What are the adverse effects

- Reduced cardiac output state due to vasoconstriction
- Heart failure or MI
- GI disturbance
- Hyponatraemia - longer term use

8. **Antiemetics**

Name some antiemetics used in the emergency department

- Ondansetron
- Metoclopramide
- Prochlorperazine
- Antihistamine
- Droperidol
- Som benzodiazepines

Compare the mechanisms of action of ondansetron and metoclopramide

These drugs are both antiemetics but act on different receptors

Ondasetron: Peripheral 5HT3 blockade (reduces vagal and spinal afferents and sensory visceral output) + central 5HT3 blockade (inhibits the vomiting centre in the chemoreceptor trigger zone (CTZ))

Metoclopramide: D2 Blockade in the CTZ. ALso a prokinetic which increased oesophageal motility and promotes gastric emptying.

Describe the potential adverse effects of metoclopramide

Most of these relate to central dopamine antagonist action

- *CNS:* restlessness, drowsiness, insomnia, anxiety, agitation. These are common, occuring in 20% of people especially the elderly.
- *Extrapyramidal effects:* acute dystonia, akathisia, parkinsonian effects (more likely with higher doses). Tardive dyskinesia can occur with chronic dosing
- *Endo:* Hyperprolactinaemia, leading to galactorrhoea, gynacomastia, impotence and menstruation disorders.

What are the doses and route of ondansetron?

4-8mg Sublingual, oral, subcut or IM

What are the potential adverse effects of ondansetron?

Headache, dizziness, constipation, diarrhoea

Uncommonly can cause a small prolongation of QT interval

In which disease states would you need to modify the dosing?

Hepatic failure

9. **Proton pump inhibitors**

Describe the MOA of PPIs

Irreversibly inactivates H/K/ATPase, blocking the proton pump, inhibiting >90% of acid secretion, for up to 24hours which is the time it takes to synthesis new pumps

Why is an IV infusion preferred to a single bolus dose?

It only inactivates actively secreting acid pumps (<10% in fasting patients)
Single dose only suppresses acid secretion for a few hours

Regarding oral formulations of proton pump inhibitors, please describe strategies used to increase their bioavailability and activity.

- PPIs are taken as prodrugs
- They have an acid resistant enteric coating to prevent gastric elimination
- Food decreases the bioavailability so its advised that people take them on an empty stomach
- They are weak bases so pass into the acidified parietal cells where they bind to H/K ATPase
- Peak activity occurs in one hour, so best to have 1 hour before a meal