Primary Cast Episode 11 - Neuro Pharmacology

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1. **Cholinergic Pharmacology: Atropine**

What is the MOA of atropine?

- A competitive, reversible muscarinic ACh receptor antagonist
- Anticholinergic activity
- Equipotent at M1, M2, M3 receptors. Minimal effects at nicotinic receptors,

Describe the pharmacokinetics of atropine

- Administration: IV, oral, topical, nebulized/inhaled
- Distribution: wide Vd including into the CNS
- Metabolism & excretion: Half life of 2 hours, 60% is excreted unchanged via the kidneys. 40% undergoes phase I and phase II metabolism and is then renally excreted

Describe the organ effects of atropine

- Eye - mydriasis and cycloplegia
- CNS - delirium, decreased tremor in parlinsons
- CVS - tachycardia (dose dependent, some small doses can cause initial bradycardia)
- Resp - bronchodilation and decreased secretions
- GIT - decreased saliva, decreased gastric acid secretion, decreased mucin production, delayed gastric emptying, decreased gut motility and resulting increased transit time
- Urinary - relaxes ureteric and bladder wall smooth muscle, urine retention
- Skin - decreased sweating

What is atropine used for clinically?

- Treatment of symptomatic bradycardia or other bradyarrhythmias - especially if vagally mediated,
- Used in ophthalmology for inducing mydriasis
- Occasionally used as an adjunct in RSI for paediatrics
- Drying of secretions in cholinergic exposure or in palliative care
- Travellers diarrhoea

Describe the effects of atropine poisoning.

- Agitation and delirium (Mad as a hatter)
- Raised temp (hot as Hades)
- Blurred vision/mydriasis (Blind as a bat)
- Flushed skin (red as a beet)
- Dry mouth (Dry as a bone)
- Tachycardia

See a flashcard from LITFL here

2. **Benztropine**
   A 40 yr old man develops a dystonic reaction following a metoclopramide injection. How does metoclopramide cause this dystonic reaction?
   Metoclopramide is a dopamine antagonist and causes an imbalance in the anticholinergic/dopamine transmission in the basal ganglia

   You treat this dystonic reaction with benztropine. What is the mechanism of action?
   Benztropine is a centrally acting antimuscarinic agent.
   Blocks the muscarinic cholinergic receptors, to reduce the imbalance in the signalling that causes the dystonic reaction

3. **Indirectly acting cholinomimetics (Acetylcholinesterase inhibitors)**
   What is the MOA of indirectly acting cholinomimetics
   - These inhibit the acetylcholinesterase enzyme thereby increasing the concentration of ACh in the vicinity of cholinoreceptors.
   - Action on both nicotinic and muscarinic receptors.

   What types of agents are there?
   - Reversible - neostigmine, physostigmine, pyridostigmine
   - Irreversible - organophosphates and insecticides

   What are the cardiovascular effects of these drugs?
   - Both sympathetic and parasympathetic ganglia can be activated
   - Parasympathetic effects generally predominate - bradycardia, decreased CO, decreased contractility and no major change in BP
   - Overdose may cause a tachycardia and hypotension

4. **Adrenergic Pharmacology: Adrenaline**
   Your patient has an allergic reaction that requires adrenaline
   Describe the pharmacokinetics of adrenaline
   - Administration: IM, IV, subcut, nebulised. Poor oral absorption.
   - Distribution: Crosses the placenta but does not cross blood brain barrier. 50% protein bound. Onset of action in seconds, duration of 2 mins.
   - Metabolism: terminated by metabolism in sympathetic nerve terminals by COMT and MAO. Circulating adrenaline metabolised by COMT.
   - Elimination: metabolites excreted in the urine.

What are the pharmacodynamic effects of adrenaline?
Equal effects at alpha and beta receptors

- Alpha = vasoconstriction
- B1= positive inotropic and chronotropic effects
- B2= smooth muscle relaxation in airways and skeletal muscle

Describe the effects of adrenaline on other organs besides the heart

- Respiratory - bronchodilation
- Eyes - pupil dilation, decreased IOP and production of aqueous humour
- Gastric smooth muscle - relaxation
- Genitourinary - bladder smooth muscle relaxation
- Liver - enhanced glycolysis
- Increased production of sweat at apocrine glands

What are some undesired complications of an adrenaline infusion?

- General - anxiety, tremor, nausea, pallor, vomiting
- Heart and circulation - palpitations and arrhythmias, myocardial ischaemia, HTN
- Metabolic - hyperglycaemia, lactic acidosis, hypokalemia

5. **Noradrenaline.**
   Your patient is hypotensive. A noradrenaline infusion is commenced.
   What receptors does noradrenaline act on?
   - Predominantly alpha 1 → vascular smooth muscle constriction
   - Also some alpha 2 activity (presynaptic) which exerts negative feedback on noradrenaline release
   - There is some effect on beta 1 and 2

   How does noradrenaline increase the blood pressure?
   - Increase is in both systolic and diastolic blood pressure
   - Alpha 1 activity → vasoconstriction → increased total peripheral resistance → increased diastolic blood pressure
   - Beta 1 activity → increased myocardial contractility → increased systolic BP

   How does norad affect the heart rate?
   - Beta 1 activity causes an increased heart rate.
   - However, the compensatory baroreceptor reflex causes a decrease in HR.
   - Overall, there is a minimal change in HR.

6. **Metaraminol**

   You are treating a patient with neurogenic shock and decide to use metaraminol.

   What is the MOA of metaraminol?

   Direct alpha 1 agonist - though there is some indirect effect via increased noradrenaline release

   What are its effects on the cardiovascular system?

   - Vaso and arterio constriction in vascular beds
   - Arterioconstriction causes an increase in BP
   - Direct cardiac effects are less important
   - HR slows due to vagal feedback
   - CO is mostly unchanged

   What role do sympathomimetics play in the management of shock?

   Temporising measures only, used whilst other treatments are instituted i.e. antibiotics, fluid replacement

   Useful in conditions where there is 'failure' of the sympathetic NS i.e. in a spinal injury or in anaesthesia

7. **Local anaesthetics**

   What classes of local anaesthetic are used in ED?

   - Aminoamides -(two i's) Lignocaine, bupivicaine, prilocaine.
   - Aminoesters - (single i) Procaine, Benzocaine, Tetracaine

   Describe the mechanism of action of lignocaine

   - Sodium channel blocker.
   - Class 1B antiarrhythmic.
   - Local anaesthetic.
   - Blocks voltage gated sodium channels without altering the resting membrane potential.

   What is the maximum safe dose of lignocaine for local anaesthesia?

   - Without adrenaline 3mg/kg
   - With adrenaline 7mg/kg

   What factors affect absorption of lignocaine after local infiltration?

   - Dose
   - Site of injection
   - Drug-tissue binding
   - Blood flow through the tissue
   - Use of adrenaline

What are the toxic effects of lignocaine?

By system:

- CNS
    - Early: perioral or tongue numbness, metallic taste
    - Moderate: nystagmus, tinnitus, muscle twitching, nausea, vomiting
    - Severe: seizures, sedation
- CVS
    - Arrhythmias i.e. bradycardia, conduction blocks
    - Hypotension
    - Worsening of CCF
    - Cardiovascular collapse
- GIT
    - Vomiting, anorexia, nausea
- Haem:
    - Methaemoglobinaemia (most often associated with prilocaine)
- Allergy
    - Rare but not impossible

8. **Nitrous**

Explain the solubility characteristics of nitrous oxide

- Low solubility in the blood so reaches arterial tension rapidly.
- Rapid equilibrium in the brain and fast onset of action and fast recovery

What is the MOA of nitrous?

Multiple actions

- Modulates GABA-A receptors
- Increases dynorphin release
- NMDA agonist

What are the organ effects of nitrous oxide?

- CNS: analgesia, amnesia, increased cerebral blood flow
- Renal: decreased GFR, increased renal vascular resistance
- CVS: dose dependent myocardial depression
- Resp: reduced response to carbon dioxide ad hypoxia
- GI: Nausea and vomiting

9. **Propofol**

Please describe the pharmacokinetics of propofol

- Administration: IV only - as a bolus or an infusion
- Distribution: Rapid onset and recovery is driven by redistribution of the drug from the brain to other areas. Distribution half life is 2-4 minutes, elimination half life up to 25 mins,
- Metabolism: rapidly metabolised in the liver.
- Elimination: Excreted in the urine as inactive metabolites.

What are the indications for propofol?
Induction agent, maintenance of anaesthesia, procedural sedation.

What properties of propofol make it suitable for procedural sedation?
Rapid onset and offset

What is the usual induction dose?
1-2.5mg/kg in adults, 2.5- 3.5mg/kg in kids

What are the clinical effects of propofol?
- Anaesthesia/sedation (no analgesia)
- Transient apnoea
- Decreased blood pressure
- Anti-emetic properties

What are the adverse effects of propofol?
Related to the system effects
- Hypotension from vaso and veno dilation and the negative inotropic effect
- Apnoea - dose related central depression of respiratory drive
- Pain on injection
- Allergy/anaphylaxis
- Propofol infusion syndrome (a metabolic acidosis)

How can these adverse effects be minimised?
- Titration of small doses
- Not using opiates or benzos concurrently
- Using an IV fluid bolus
- Reduce dose in elderly or those with poor cardiovascular reserve

10. Ketamine

Describe the pharmacodynamics of ketamine
- NMDA receptor antagonist
- Inhibits reuptake of catecholamines and serotonin
- Potent short acting sedative, amnestic, analgesic and anaesthetic agent

What are the pharmacokinetics of ketamine?
- Absorption: Highly lipid soluble, so rapid onset
- Distribution: Effect is terminated by redistribution to inactive tissue sites. Low protein binding.
- Metabolism: Metabolised in the liver via cytochrome P450 enzymes to inactive metabolites
- Elimination: metabolites are excreted in the urine

What are the system effects of ketamine?

- CNS: dissociative anaesthesia, profound analgesia. Cerebral vasodilation. Potential anticonvulsant properties.
- CVS: hemodynamically stable, increases HR, BP, CO and myocardial oxygen consumption
- Respiratory: Maintains airway reflexes, minimal respiratory depression, bronchodilator effects. Can cause lacrimation and laryngospasm in children,
- Ocular: nystagmus

What are the adverse effects of ketamine?

- Related to the system effects
- CNS- emergence phenomenon, dysphoria, hallucinations
- GI - nausea, vomiting
- Respiratory - laryngospasm, increased salivation

Aside from procedural sedation, what are some other indications for ketamine?

- Induction agent
- Bronchodilator effect in asthma
- Acute behavioural disturbance

What is an appropriate IV dose for induction or sedation?
1-2mg/kg

What are the main differences between ketamine and propofol?

- Propofol causes a marked decrease in peripheral BP, whereas ketamine is hemodynamically stable on induction
- Ketamine has a slower recovery and is associated with emergence phenomena

11. Thiopentone (included only to illustrate what to do if you get a question that you don't really know the answer to but you vaguely know the drug)
What are the pharmacokinetics?

- IV bolus
- Rapidly crosses BBB
- Highly lipid soluble
- Redistributes to muscle and fat
- Metabolised in the liver
- Excreted by the kidney

What are the advantages of thio?
Rapid onset, amnesic, reduction in ICP, anticonvulsant properties

What are the adverse effects?
Drops BP, SV, CO due to myocardial depressant effect and increased capacitance
Apnoea

12. Neuromuscular blockers: Suxamethonium

What is the MOA of sux?

Depolarizing neuromuscular blocker - 2 acetylcholine molecules linked end to end
2 phases

- Phase I (depolarising)
    - Reacts with nicotinic receptor to open the channel
    - Depolarises the motor endplate with spread to adjacent membranes
    - Causes fasciculation
- Phase II (desensitising)
    - Continued or repeated exposure to sux
    - End plate depolarisation increases
    - Membrane repolarizes but cannot be depolarised because it is now desensitised
    - Means it is unresponsive to subsequent impulses
    - Causes a flaccid paralysis

What are the pharmacokinetics of suxamethonium?

- Administration: IV
- Distribution: rapid onset (30-60 seconds) short duration (2-8 minutes)
- Metabolism: Hydrolysed rapidly by plasma pseudocholinesterase

What are the adverse effects of sux?

- Muscle pain from fasciculations
- Bradycardia (with repeated doses)
- Release of K+, especially in burns, trauma
- Raised IOP and raised ICP
- Risk of malignant hyperthermia
- Risk of prolonged paralysis in cases of reduced or abnormal cholinesterase

13. Rocuronium

What is the MOA of rocuronium?

- A nondepolarizing neuromuscular blocker
- Competitive inhibitor of acetylcholine at the nicotinic receptors
- In large doses is can enter the pore of the ion channel and cause a stronger block

What are the pharmacokinetics?

- Absorption: Given as an IV bolus 1.2mg/kg, onset within 45-60seconds.
- Distribution: Rapid. Highly ionized, small Vd. Duration of 20-75 mins.
- Metabolised in the liver, short half life
- Eliminated in the urine

How does suxamethonium differ from rocuronium?

- Duration of action of sux is much shorter (5-10 mins)
- Different side effect profile and contraindications
- Sux is a depolarizing NMB, whereas roc is a non depolarising
- Rocuronium has an antidote
- Suxamethonium metabolised in the plasma, roc in the liver

14. Ethanol

Your patient is intoxicated.

What are the pharmacodynamic effects of ethanol?

- CNS: sedation, disinhibition, impaired judgement, impaired motor skills, ataxia, slurred speech, coma, respiratory depression.
- CVS: decreased contractility
- Smooth muscle vasodilation = hypothermia

Describe the pharmacokinetics of ethanol

- Absorption: rapidly absorbed from the GIT (water soluble)
- Distribution: Rapid, Vd is total body water
- Metabolism: mostly in the liver by alcohol dehydrogenase via zero order kinetics
- Excretion: Lungs, urine.

What does zero order kinetics mean?

Elimination occurs at a constant rate, independent of the drug concentration

What drugs have zero order kinetic metabolism?

Phenytoin, theophylline, warfarin, salicylate, heparin.

15. Benzos

What is the MOA of benzodiazepines?

Binds to components of the GABA- A receptor in neuronal membranes in the CNS.
This receptor is a chloride ion channel.
Benzodiazepines enhance GABAs effects without directly activating the channel.
This causes an increased frequency of channel opening.

What are the organ level effects of diazepam?

- Sedation - calming effect, anxiolysis at low doses. Can also cause psychomotor and cognitive depression, amnesia
- Hypnosis and anaesthesia at higher doses.
- Anticonvulsant effects
- Muscle relaxation
- Respiratory and cardiovascular depression - especially at high doses or in those with CCF/chronic heart disease or in hypovolemic states

What are the uses of diazepam in the ED?

- Anticonvulsant
- Sedation of an agitated patient
- Withdrawal states - alcohol, benzodiazepines
- Various toxidromes to prevent seizures

16. Antiepileptics: Carbamazepine

What is the mechanism of action of carbamazepine?

- Sodium channel blockade
- Binds to those in an inactive state and stabilises them there
- Inhibits high frequency repetitive firing neurons - so no interference with baseline or normal activity

What are the pharmacokinetics?

- 100% oral bioavailability
  Peak levels 6-8 hours
- 70% protein bound
- Low clearance - 36 hour half life initially which decreases over time
- Induces its own metabolism via P450 enzyme effect so dose increase required in the first few weeks of treatment

What are the adverse effects?

- Ataxia, diplopia
- Sedation at high doses
- Blood dyscrasias - aplastic anaemia, agranulocytosis
- Skin rash
- Drug interactions with other P450 metabolised drugs i.e. phenytoin.

Note: *I found it impossible to remember anything to do with carbamazepine until I made up the following story for a memory aid "Don't have a seizure in the car eating salty chips" i.e. Antiepileptic, CARbemazapine, Sodium channels, high oral bioavailability.*

17. Phenytoin

Describe the pharmacokinetics of phenytoin

- Given oral or IV, High oral bioavailability, not well absorbed IM
- Peak serum concentration at 3-12 hours
- Highly plasma protein bound with moderate volume of distribution
- Metabolised in the liver to inactive metabolites and then renal excretion
- Elimination is dose dependent - lower concentrations is first order kinetics, but enzymes become saturated at high concentrations and metabolism shifts to zero order kinetics
- As a result, the half life is variable

What is the MOA of phenytoin?

- Sodium channel blockade
- Prolongation of the inactive state of the Na channel
- Als o enhances GABA release
- These actions work to inhibit the generation of rapidly repetitive action potentials

What is the rationale for using a loading dose of phenytoin?

- Need 4 half lives to reach steady state, which would take 5-6 days
- So to reach target concentration more rapidly, we use a loading dose.

What are the risks associated with IV phenytoin administration?

- Hypotension and bradycardia with rapid infusion - can cause cardiovascular collapse
- Local necrosis if there is extravasation
- Purple glove syndrome - black discoloration distal to the IV site

What are the adverse effects of phenytoin use?

- Nystagmus and loss of smooth pursuits is normal with therapeutic levels and not concerning
- Anyone with diplopia and ataxia needs a decrease in their dose
- Gingival hyperplasia and hirsutism can occur over long term use, as can abnormal rashes, osteomalacia and low vitamin D
- Can cause foetal abnormalities if used in pregnant people
- Sedation, coma, cerebellar toxicity are associated with toxic levels.

18. Keppra

What is the mechanism of action of levetiracetam?

- Binds the the SV2A synaptic vessel protein
- Undergoes endocytosis and binds in the vesicle
- Prevents release of glutamate during increased frequency activity

What are the pharmacokinetics?

- Given orally or IV, rapid oral absorption in just over an hour
- Low protein binding
- Half life 6-8 hours so BD dosing
- ⅔ excreted unchanged in the urine
- ⅓ is deaminated in the blood
- NO liver metabolism = minimal interactions when compared to other antiepileptics

What are the side effects?

- Mild: somnolence, ataxia, dizziness
- Worse: behavioural and mood changes - aggression/anxiety

What is the dose for status epilepticus?

- Paeds - 40mg/kg IV/IO up to 3g
- Adults 60mg/kg IV/IO up to 4.5g

19. Na Valproate

What is the mechanism of action of valproate

Unknown, could be action on GABA channels, Na channels or NMDA receptors
Works on a number of different epilepsy models and the clinical effect doesn't seem to be associated with serum drug levels.

What are the adverse effects?

- Mild: Can cause nausea, vomiting, abdominal pain
- Severe: cerebral oedema and coma
- Hepatic toxicity including acute liver failure (more common in patients under 2 yrs old)
- Thrombocytopaenia and bruising from bone marrow depression
- Neural tube defects if used during pregnancy
- Hyperammonaemia leading to sedation
- Lots of drug interactions - inhibits metabolism of several drug via inhibition of the P450 enzyme system. Directly displaces phenytoin from plasma proteins, increases levels of carbamazepine and decreases the clearance of lamotrigine.

20. Antidepressants:SSRIs and serotonin syndrome

Describe the mechanism by which serotonin syndrome occurs

- Excessive stimulation of serotonin receptors in the CNS due to overdose of a single drug or concurrent use of several drugs.
- Predictable rather than idiosyncratic.

How do drugs cause excessive stimulation of serotonin receptors?

- Inhibition of serotonin metabolism - i.e. amphetamines, moclobemide
- Prevention of serotonin reuptake in nerve terminals - fluoxetine, sertraline, venlafaxine, tramadol, TCAs
- Serotonin release or increased intake of serotonin precursors - tryptophan, lithium

21. TCAs

What is the MOA of tricyclic antidepressants?

- Inhibition of serotonin and noradrenaline reuptake
- This increases the amount of serotonin and noradrenaline in certain parts of the brain and spinal cord.
- Based on the monoamine hypothesis for depression, this leads to improved mood and can alleviate neuropathic pain

- TCAs also block sodium channels, potassium channels, muscarinic (M1) receptors, Histaminic (H1) receptors and postsynaptic alpha 1 adrenergic receptors

What are the pharmacokinetics of tricyclics?

- Well absorbed orally
- Bioavailability 40-50%
- Long half life
- High first pass metabolism
- High protein binding
- High lipid solubility
- Large volume of distribution
- Metabolised in the liver with active metabolites

What clinical manifestations would be seen in an overdose of tricyclic antidepressants?

Can be divided into important systems - cardiac, CNS, and then other anticholinergic symptoms

Cardiac

- Tachycardia
- Hypotension (from alpha 1 blockade)
- ECG changes - prolonged PR, wide QRS (Na block) long QT (K block) VT, VF

CNS

- Drowsiness
- Delirium (from anticholinergic effects)
- Seizures
- Coma

Other Anticholinergic Effects

- Agitation
- Mydriasis
- Warm, dry, flushed skin
- Urinary retention
- Ileus

How does the volume of distribution of TCAs influence their toxicity?

TCAs have a large Vd and tissue concentrations are high, especially in well perfused organs such as the brain and the heart.

What therapies for TCA toxicity might reduce their tissue distribution?

Alkalinisation - bicarb or hyperventilation

Increases plasma protein binding of the free drug, removing it from the tissues and reducing its toxicity

22. Lithium

Describe the pharmacokinetics of lithium

- Oral administration, rapid and near complete absorption. Peak concentrations at 1-2 hours but complete by 6-8 hours.
- Volume of distribution is in total body water - very slow distribution from extra to intracellular compartments
- No protein binding
- No metabolism
- Excreted unchanged in the urine - 20% of the creatinine clearance
- Plasma half life is 20 hours

What factors may influence lithium excretion?

- Renal function - slowing down of the GFR = more time in the PCT for reabsorption
- Water and sodium status - lithium can be reabsorbed in place of sodium in water/sodium depleted states
- Drug interactions that reduce or enhance clearance
- Serum concentration to begin with

What are some drug interactions with lithium?

- Thiazide diuretics - cause a reduction in lithium clearance
- Newer NSAIDs also reduce clearance
- Osmotic or loop diuretics actually increase clearance

What are the toxic effects of lithium?

- Neuro: tremor, ataxia, dysarthria, confusion
- Thyroid: reversible hypothyroidism
- Renal: polyuria, polydipsia via nephrogenic diabetes insipidus
- CVS: oedema
- Pregnancy: category D, causes Ebstein's anomaly (a congenital cardiac malformation)

How do you assess and treat lithium toxicity?

- Measure lithium levels (10-12 hours after the last dose)
- Treatment is supportive, dialysis

23. Antipsychotics

By what route can olanzapine be administered?

Oral (tablet or wafer), parenteral with short acting IM or long acting depot injection

What is the predominant mechanism of action of atypical antipsychotic medication?

- Serotonin receptor antagonism
- There is also a weaker effect on dopamine receptor antagonism (D2)

What are the adverse effects of atypical antipsychotics?

- Sedation
- Extrapyramidal reactions - less common that with the typical antipsychotics
- Tardive dyskinesia, akathisia
- Antimuscarinic effects - dry mouth, urinary retentions
- Orthostatic hypotension
- Weight gain
- Hyperglycaemia
- Hyperprolactinaemia
- Agranulocytosis (seen with clozapine)
- Neuroleptic malignant syndrome

24. Dopamine: Levodopa

Why is levodopa used in combination with carbidopa?

- Carbidopa is a peripheral dopa decarboxylase inhibitor
- Because it doesn't penetrate the BBB, it reduces the peripheral metabolism of levodopa which leads to increased half life and more dopa being available to enter the CNS to exert its effects

What are the adverse effects of levodopa?

- GIT: anorexia, nausea, vomiting is common due to stimulation of the emetic centre in the brainstem
- CVS: arrhythmias due to increased peripheral formation of catecholamines
- Dyskinesias: can occur in 80% of people receiving this treatment long term
- Behavioural change: depression, anxiety, agitation, insomnia, nightmares
- Other miscellaneous: gout, abnormalities to taste and smell, abnormal LFTs

25. Serotonin: Triptans

How does sumatriptan work in the treatment of migraine?

- Migraine thought to arise secondary to vasodilation of cerebral meningeal blood vessels
- Triptans are selective agonists for 5HT-1 receptors found on these vessels
- Cause vasoconstriction, preventing symptoms

What are the pharmacokinetics?

- Bioavailability is low or varied (10-70%)
- So given subcut or intranasal more often than orally
- Half life is 2-3 hours so frequent daily dosing

What are the pros and cons of sumatriptan use?

- Pros: only usually mild side effects (tingling, weakness) usually very effective
- Cons: contraindicated in patients with IHD due to coronary spasm risk, short duration of effect so requires multiple dosing. Very expensive.