Primary Cast Episode 16 -
Analgesic & Anti-Inflammatory Pharmacology

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1. **Aspirin**

Outline the mechanism of action of aspirin

- Irreversible non selective cyclooxygenase inhibitor (COX 1 and 2)
- Inhibits platelet aggregation through reduction of thromboxane A2 (COX-1 inhibition), effect lasts for the life of the platelet (10 days)
- Inhibits prostaglandin synthesis in tissues (COX-2) resulting in the anti-inflammatory, analgesic and antipyretic effects.

Describe the pharmacokinetics of aspirin

- *Absorption:* Rapid due to pKa of 3.5, hydrolysed to salicylic acid in the blood, peak plasma level in 1-2 hours
- *Distribution:* Low protein binding, small volume of distribution
- *Metabolism:* Metabolised by esterases in tissues and plasma. Saturable metabolism with increasing doses – switches from first order to zero order kinetics. Half-life of 15 mins but clinical effects last longer due to irreversible binding.
- *Elimination:* Metabolites cleared in the urine – increased elimination in more alkaline urine

Outline the adverse effects of aspirin

- GI—nausea & vomiting, GI bleeding from gastritis or peptic ulceration, hepatotoxicity
- Hypersensitivity reactions – asthma, oedema, rash
- Bleeding – can be prolonged due to platelet inhibition
- CNS—headache, tinnitus, dizziness
- CVS—fluid retention, oedema
- Renal impairment

2. **Ibuprofen**

Describe the pharmacodynamics of ibuprofen

- Ibuprofen is a NSAID
- Inhibition of prostaglandin biosynthesis via REVERSIBLE inhibition of COX
- Anti-inflammatory, antipyretic and analgesic effects

Describe the pharmacokinetics of ibuprofen

- *Absorption:* Well absorbed orally
- *Distribution:* Highly protein bound, small volume of distribution
- *Metabolism:* in the liver by cytochrome P450 enzymes
- *Elimination:* renal, serum half life 1-3 hours

3. **Colchicine**

Describe the mechanism of action of colchicine

- Anti inflammatory effect via binding to tubulin, inhibits WBC migration and phagocytosis
- Inhibits formation of leukotrine B4
- No effect on uric acid metabolism

What are the indications for colchicine?

- Treatment of acute episodes of gout
- Prophylaxis of recurrent episodes
- Can also be used in familial mediterranean fever
- Sometimes prescribed in pericarditis

4. **Paracetamol**

Describe the pharmacokinetics of paracetamol

- *Absorption:* Rapid, bioavailability 70-90%, peak concentration at 30-60minutes. Given PO, IV, PR
- *Distribution:* Low protein binding, widely distributed but not into fat
- *Metabolism:* Hepatic, first order kinetics. >95% undergoes glucoronidation and sulfation, 5% undergoes metabolism via CYP450 mechanism (phase 1 reaction – hydroxylation) to form NAPQI. NAPQI is toxic but is usually detoxified by glutathione. Half life 2-3 hours
- *Elimination:* <5% is excreted unchanged in the urine

What is the toxic dose of paracetamol?

150-200mg/kg in an adult

Describe the mechanism by which paracetamol causes toxicity

- Paracetamol is usually conjugated with glucuronide and sulphate by transferase enzymes
- This pathway becomes saturated in overdose, allowing increasing paracetamol to be metabolised by the smaller pathway to NAPQI
- NAPQI is detoxified by glutathione, which becomes depleted, resulting in high levels of the toxic metabolite

What are the clinical features of paracetamol toxicity?

- Nausea, vomiting, abdominal pain
- HAGMA
- Liver failure
- Renal failure (acute tubular necrosis)
- In massive doses can cause decreased level of consciousness and coma

How does N-acetyle-cysteine work in the treatment of paracetamol overdose?
4 mechanisms:

- Sulfhydryl group donor – restores hepatic reduced glutathione levels
- Acts as an alternative substrate for conjugation with toxic metabolite
- Provision of inorganic sulphate
- Reduction of NAPQI back to paracetamol

What are the adverse effects of N-acetylcysteine?
Mild anaphylactoid reactions in 15-20% of people, causes flushing, rash and angioedema

5. **Fentanyl**

Describe the mechanism of action of fentanyl
Synthetic opioid that acts as an agonist at the μ (mu) receptor

Describe the pharmacokinetics of fentanyl

- *Absorption:* Can be given transdermal, IV, subcut, sublingual/buccal (lozenge), transdermal patch and via epidural.
- *Distribution:* Highly lipid soluble, crosses the blood brain barrier
- *Metabolism:* High first pass metabolism, metabolised by P450 enzymes with no active metabolites
- *Elimination:* Excreted in the urine with <5% unchanged. Elimination half life is 7 hours due to lipid solubility

What is the potency of fentanyl relative to morphine?
100 times more potent 0.1mg (or 100 micrograms) fentanyl equivalent to 10mg morphine

What are the adverse effects of fentanyl?

- Respiratory depression, cough, chest wall and laryngeal rigidity
- Nausea, vomiting, constipation
- Dysphoria
- Urticaria, itch
- Urinary retention

6. **Morphine**

What is the mechanism of action of morphine?
Acts on mu/delta/kappa receptors to reduce presynaptic and postsynaptic neurotransmission.

Outline the pharmacokinetics of morphine

- *Absorption:* Can be given orally, or parenterally. Oral bioavailability is 80-100% but it has a high first pass metabolism so PO doses are larger.
- *Distribution:* Volume of distribution 5L/kg

- *Metabolism:* Conjugated in the liver to mostly morphine-3-glucoronide. Small amount (10%) is metabolised to morphine-6-glucoronide, which has an increased analgesic potency
- *Elimination:* metabolites, via the kidneys. Half life of 2-3 hours.

What are the CNS effects of morphine?

- Analgesia
- Sedation
- Respiratory depression
- Euphoria
- Cough suppression
- Miosis
- Truncal rigidity
- Nausea/vomiting

Why do opiates cause respiratory depression?

Inhibition of brainstem respiratory controls, allowing less response to hypercapnoea

7. **Oxycodone**

Outline the pharmacodynamics of oxycodone

Opioid agonist that acts on mu receptors in the brain and spinal cord.

Outline the pharmacokinetics

- *Absorption:* Good oral absorption
- *Distribution:* High volume of distribution
- *Metabolism:* Low first pass metabolism compared to morphine, duration of action 3-4 hours, metabolised by P450 enzymes
- *Elimination:* Metabolites excreted by the kidneys

What strategies may be used when prescribing oxycodone to reduce the risk of developing dependence?

- Establish goals of care at the start of treatment
- Combine with non-opioid analgesics
- Smaller doses at longer intervals
- Use of controlled release preparations
- Frequent re-evaluation of ongoing requirements

8. **Opiate dependence**

What are some drugs that are used in the treatment of opioid dependence?

- Methadone
- Buprenorphine
- Clonidine
- Naltrexone
- Naloxone

Outline the principles behind how these drugs work

- *Methadone* – longer acting opiate agonist, orally active, used to stabilise and gradually reduce over time given longer half life
- *Buprenorphine*- partial opioid agonist that can be given once daily. Low doses for detox and higher doses for maintenance
- *Clonidine* – centrally acting sympatholytic agent that mitigates the sympathetic overactivity seen in withdrawal
- *Naltrexone* – used after patient has detoxified as it is a long acting pure opiate antagonist
- *Naloxone* – short acting opiate antagonist, used in overdose as a rescue medication.

What problem can be associated with naloxone administration?

- Rapid precipitated withdrawal
- Re-sedation due to short half life

How can these problems be minimised?

- Using smaller, titrated doses
- Naloxone infusion