Pharmacology for Pharmacists

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MOA - 3 type of Opioid recep (just know 3 A/E is- N&V, constipation). All analgesic

- Mu (μ): Analgesia, Respiratory depression, Euphoria, sedation, Miosis, N&V Constipation, physical dependence, urinary retention
- Delta (δ): Analgesia (spinal), Respiratory depression, N&V
- Kappa (κ): Analgesia, N&V, sedation, Miosis, Dysphoria

- Action
  Opioid agonist binds to opioid recep → inhibit adenylyl cyclase → ↓ cAMP → which causes
  - close Ca channel- cause inhibit NT release
  - open K channel- cause hyperpolarisation therefore no depolarisation, which means no transmission

Pharmacological effects of opioid agonists

CNS effects
- Analgesia
- Respiratory depression – common cause of death in opioid overdose
  - Is due to ↓ in sensitivity of the respiratory centre to the stimulation by CO2
- Sedation (promote sleep)
- Miosis diagnostic of an opioid overdose
  - Only constipation and miosis cannot get tolerant to hence miosis used check for overdose
- N&V (via affecting chemoreceptor trigger zone)
- Dysphoria (k)- depressed or euphoria (μ)- elated happy
- Inhibition of cough reflex e.g codeine used as cough suppres
- Physical dependence

Cardiovascular effects
- ↓ myocardial oxygen demand
- Vasodilation which → • hypotension, (via affecting vasomotor centre)

GI effects
- Constipation (decreased GI motility & parasymp tone)
- Nausea and vomiting - by triggering CTZ (chemoreceptor trigger zone)

Genitourinary effects
- Increased bladder sphincter tone
- Urinary retention

Neuroendocrine system effects by affecting pituitary gland
- Inhibition of release of luteinizing hormone
- Stimulation of release of antidiuretic hormone and prolactin

Immune system effects
- Suppression of function of NK cells T-cells (hence heroin addicts ↑ disease)

Dermal (skin) effects due to cause Mast cell to release histamine
- Flushing (redden) • Pruritus (itchy)
- Urticaria (hives i.e drug rash get pink/red itchy wheals) or other rash

A/E of opioids
- Respiratory depression- Tx by IV opioid antagonist, naloxone
- Sedation and drowsiness
- Hallucinations, confusion
- N&V, Constipation due to Stimulation of the chemoreceptor trigger zone in the medulla
- Rashes, pruritis, flushing- Opioids cause mast cells release of histamine
- Flushing reaction - redness and a feeling of warmth over the upper torso

Classification of opioid drugs

Strong Agonist- morphine-acute/chronic pain come in sustained release and short acting 2-3 hr, methadone (used as maintenance for addicts, long ½ t so only 1d), oxycodone
Partial agonist - buprenorphine
Opioid antagonist (block recep) - naloxone, naltrexone. Other opioid agonist - tramadol

Weak agonist mild-moderate pain

- **Codeine:** Given orally for mild to moderate pain
  - Analgesic effect depends on it being metabolised into to morphine by the CYP2D6 enzyme. [10% Caucasians, 1-2% Asians lack CYP2D6 so no effect]
  - Effect and A/E similar to low-dose morphine (~ 1/20 potency) like nausea and constipation

- **Dextropropoxyphene:** Is derivative of methadone
  - Analgesic efficacy ~½ codeine
  - A/E: respiratory depression, neurotoxicity and acute heart failure (i.e. affect heart, brain & lung). Its metabolite (nordextropropoxyphene) can cause dizziness, confusion and cardiac dysrhythmias
  - Avoid use in renal impairment- as it and its metabolite accumulate when renal clearance is slow
  - Caution when used in elderly as t½ in elderly patients can be long so can cause CNS A/E - confusion, dizziness.

Other opioid agonist: as work different

**Tramadol:** A metabolite of antidepressant trazodone

- Effect= Binds to mu-receptors get agonist effect. Also weakly inhibits the reuptake of NA and 5-HT neurotransmitters.
- Has Morphone-like pharmacological actions but Lower risk of constipation than morphine
- Metabolised by CYP2D6 to 6x more potent analgesia effect
- Use to avoid opioid A/E (has same SE but less effect): respiratory depression, Constipation, abuse, sedation/confusion.
- For Moderate pain, Neuropathic pain

**Opioid Addiction**
Use to get euphoric effect and chronic use get dependent and also withdrawal effects and tolerance, which cause more use. Opioids with rapid rise in brain concentration of drug – most abused as get the euphoric effect. e.g oxycodone when injected is rapidly released

- **Tx**
  - To diagnosis opioid toxification tolerance can’t be acquired to constipation and miosis (constrict pupil) so miosis is used.
  - **opioid antagonist**- naloxone, naltrexone
  - Tx opioid overdose, intoxication and dependence (also Reverse opioid-induced respiratory depression, Improve breathing of babies of mothers treated with opioid during labour)
  - A/e- withdrawal Sx expressed esp by naloxone, reverse of analgesia

- **Competitive opioid receptor antagonist** (i.e competes recep and block)

  **Naloxone:** Affects all three types of opioid receptors, has higher affinity for receptors than most opioid agonists
  - short ½ t 1-4 h
  - able reverse respiratory depression and sedation in opioid OverDose (OD)
  - Caution – relapse as short ½ t esp if methadone OD as methadone got long t½

  **Naltrexone:**
  - Tx: Maintenance of opioid addiction
  - Greater oral efficacy than to naloxone
  - Longer ½ t 10-12 hours
  - Tolerance to opioids is ↓ when used, so if attempt to redo a high amount used before → overdose

- **Opioid withdrawal syndrome**
  - psychological dependence (First 12 h after withdrawal): nervousness, sweating and craving
  - physiological (physical) dependence (after): dilated pupils, anorexia, weakness, depression, insomnia, GI and skeletal muscle cramps, ↑ respiratory rate, and diarrhoea
heroin get high effect as rapid goes blood then brain and short ½ t so get withdrawal Sx with regular use while methadone long ½ t so less withdrawal and plasma conc isn’t high enough get high effect there’s no Sx (asymptomatic)

- Tolerance can be psychological (learned) or Non-associative (adaptive) tolerance- Which is due to down-regulation of opioid receptors
  - Cross Tolerance is Tolerance to (effects) analgesia, euphoria, respiratory depression
  - Opioid rotation may overcome some problems with tolerance

**Maintenance of opioid dependence**

**Naltrexone** maintenance
- Naltrexone is a long-acting, orally effective opioid antagonist.
- Useful for those illicit opioid users who are committed to abstinence.

**Methadone**: Used as substitute for heroin and morphine addicts
- Similar effects to morphine but less withdrawal Sx and A/E
- High affinity for opioid receptors
- Reduce immediate “high” of heroin
- Not suitable for acute pain (for chronic pain) as long ½ t >24 hrs

**Buprenorphine** (orally no high effect but if injected it will have high effect)
- gives it a lower OD risk and less physical dependence compared to methadone but the lower agonist activity is not suitable for some patients.
- Is partial agonist (is very potent opioid analgesic) and antagonist properties
- Long t1/2 = 12 hours
- More marked dizziness and nausea – limits use
  - Suboxone (Buprenorphine + naloxone). Naloxone is included in tab to discourage IV use. It has no effect when used sublingually but when injected naloxone will activate & antagonise the effects of other opioids & cause withdrawal Sx

**Local Hormones**
- Signs of Inflammation
  - Heat
  - Redness
  - Loss of function
  - Swelling (oedema)
  - Pain

- Inflammatory Process
  1. Bacteria enter through cut cause release of local hormones (e.g histamine) by damaged cells → (2) they signal inflam= vasodilation-(red), ↑ permeability of BV-(swelling) → (3) blood clot forms to stop bleeding via platelets → basically WBC kill Bacteria
  2. (4) margination- where phagocytes (& WBC) stick to endothelium (IL-1, TNF-α (local mediators stimulated by Bacteria exotoxins) act on endothelial cells to express adhesive mole) →
  3. (5) migration- phagocytes squeeze out of BV and phagocytise Bacteria

**4 ENZYME cascades**- activated when substance from Bacteria like endotoxin which activate cascade
- Complement Cascade- made of C1-9
  - Enzymatic splitting of C3 to peptides C3b (opsonin) –attaches to surface of microbes & help phagocytosis & C3a (anaphylatoxin)-cause mast cells to release histamine
  - C5a – cause mast cells to release histamine, is chemotactic attractant and activates WBC
  - Finally, C5 to C9 combine to form ‘membrane attack complex’ that attaches to membranes of microbes→ LYSIS

- **CYTOKINES**
  - During inflam, cytokine are made & released by cells of IS. They regulate the inflammatory actions & other Immune System cells e.g mast cells, leukocytes, endothelial cells
  - Types of cytokines:
    - Interleukins(IL)
      - 1* pro-inflammatory (IL): Tumour necrosis factor (TNF)-α, Interleukin (IL)-1
      - Release: by many cells like macrophages during inflam
The Triple Response

1. Red skin (local vasodilatation)
2. Weal (increased permeability of post capillary venules)
3. Flare (from sensory nerve reflex, vasodilator mediator released)

- **Func:** initiate synthesis & release of secondary cytokines, e.g. Chemokines
  - IL-1, IL-6 → Fever
  - TNF-α and IL-8 → Leukocytosis (↑ no. of WBC)
  - Some ILs have anti-inflammatory effects e.g IL-4 inhibit chemokine product

**Chemokines** (chemo-attractant cytokines)
- coordinate leukocytes migration - tell where to go
- Cause mast cells release histamine
- Promote angiogenesis (form & develop. blood vessels)
- Act through G-protein-coupled receptors
- NB: Δ in expression of cytokines can cause over exaggeration of immune response → inflam disease e.g rheumatoid arthritis

**Interferons (IFN)**
- Released: by virus-infected cells
- Func: Activate antiviral mechanisms in neighbour cells
- 3 classes: IFN-α, IFN-β, IFN-γ
  - IFN-α has antitumor action & antiviral
  - IFN-β have antiviral activity
  - IFN-γ has a role in initiate Th cells-1 responses

**HISTAMINE**
- Synthesis and Storage: made from histidine by histidine decarboxylase. Found in most tissue Stored mostly in mast cells and basophil granules
- Release: by exocytosis during allergic/inflam rxn
  - Secreted when C3a and CSa interact with mem receptors or when Ag interacts with IgE fixed on mast cell
- Receptors of histamine: 4 main types: H1, H2, H3, H4 act via G-protein recep
- Actions:
  - Smooth muscle: Via H1 recep, contracts
  - Cardiovascular: H1 recep- dilates BV & H2 recep- ↑ HR, cardiac output
  - GIT: H2 recep- ↑ gastric acid secretion
  - CNS: as transmitter & H1 recep- stimulates sensory nerve endings, causing itching

**BRADYKININ (BK)=pain**
- Formation: Hageman factor activated by contact with –ve surfaces of bac LPS, collagen, etc promtes prekallikrein → kallikrein → which promtes HMW-kininogen → BK
  - During inflam, due to ↑ vascular permeability, Hageman factor, prekallikrein, kininogens leak out of vessel

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