Opioids

- Opioid
  - Compound with morphine-like activity
- Opiate
  - Substance extracted from opium
  - Exudate of unripe seed capsule of Papaver somniferum
  - Contain 2 types of alkaloids

Phenanthrene derivatives

- Morphine (10% in opium)
- Codeine (0.5% in opium)
- Thebaine (0.2% in opium), (Nonanalgesic)

Benzoisoquinoline derivatives

- Papaverine (1%)
- Noscapine (6%)

Nonanalgeslic

Opioids

- Mordern definition of opioid
  - Molecule that interact with opioid receptor
- Opioid compound
  - Opioid receptor agoninsts, antagonists, agonists-antagonists
  - Natural products, synthetic and semisynthetic compounds
  - peptides synthesized by neurone and other cell

CLASSIFICATION OF OPIOIDS

Natural opium alkaloids:

- Morphine
- Codeine

Semisynthetic opiates:

- Diacetylmorphine (Heroin)
- Pholcodeine

Synthetic opioids:

- Pethidine (Meperidine)
- Fentanyl, Alfentanil, Sufentanil, Remifentanil
- Methadone
- Dextropropoxyphene
- Tramadol

COMPLEX ACTION OPIOIDS AND OPIOID ANTAGONISTS

Agonist-antagonists (κ analgesics)

- Nalorphine
- Pentazocine
- Butorphanol

Partial/weak μ agonist + κ antagonist

- Buprenorphine

Pure antagonists

- Naloxone
- Naltrexone
- Nalmefene

Pain Pathophysiology

- Pain is an ill-defined, unpleasant sensation, evoked by an external or internal noxious stimulus.
- Analgesic relieves pain without significantly altering consciousness.
- Pain perception has 2 components
  - Nociceptive component
  - Affective component

- Most of available opioid analgesics
  - Act at μ-opioid receptor
- Activation of μ-opioid receptor

  → analgesia, euphoria, respiratory depress, nausea, vomiting, decreased gastrointestinal motility, tolerance, dependence
- δ-, κ-opioid receptor
  - analgesia
  - dysphoria, Psychotomimetic (κ)
  - Affective behaviour, proconvulsant (δ)
  - Not cause respiratory depression or to decease GI motility

    → Analgesia without μ-opioid side effect

- μ antagonist- β-funaltrexamine
- κ antagonist-Norbinaltorphimine
- δ antagonist- Naltrindole

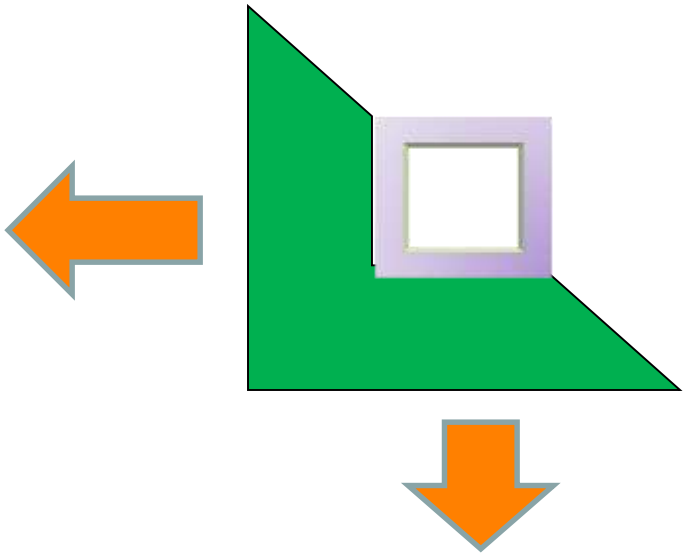
- Morphine
  - μ, δ, κ receptor activation
- Fentanyl, sufentanyl
  - More selective μ-receptor agonist
  - High effective analgesia

Endogenous Opioid Peptides

- A number of endogenous opioid peptides having morphine like activity are found in brain, pituitary, spinal cord, GIT

- β-Endorphins - μ
- Enkephalins - μ & δ
- Dynorphins- κ
- Endomorphins- μ
- Nociceptin- NOP receptor (nociceptin opioid peptide receptor)

Pharmacodynamics: CNS



Undesirable:

- Euphoria
- ↓Respiration
- Sedation
- Endocrine effects

Pharmacokinetics

- Absorption: GI tract
- Distribution: protein binding
- Biotransformation: liver
- Excretion: kidney and GI (bile)
- Differs by age, gender

Effects of Morphine

Central Nervous System Effects

Analgesia

- Pain consists of both sensory and affective (emotional) components.
- Opioid analgesics reduce both aspects of the pain experience, especially the affective aspect.
- In contrast, nonsteroidal anti-inflammatory analgesic drugs have no significant effect on the emotional aspects of pain.

Euphoria

- intravenous drug users experience a pleasant floating sensation with lessened anxiety and distress (DA release in nucleus accumbance).
- However, dysphoria, an unpleasant state characterized by restlessness and malaise, may sometimes occur.

Sedation

- Drowsiness
- clouding of mentation
- little or no amnesia
- No motor incoordination
- Sleep is induced in the elderly (can be easily aroused from this sleep)

Respiratory Depression

- by inhibiting brainstem respiratory mechanisms.
- Alveolar PCO_2 may increase, but the most reliable indicator of this depression is a depressed response to a carbon dioxide challenge.
- In individuals with increased intracranial pressure, asthma, chronic obstructive pulmonary disease, or cor pulmonale, this decrease in respiratory function may not be tolerated.

Cough Suppression

- Codeine in particular
- However, cough suppression by opioids may allow accumulation of secretions and thus lead to airway obstruction and atelectasis.

Temperature regulating centre depression

- chances of hypothermia

Vasomotor centre depression

- Fall in BP

Morphine stimulates:

- CTZ (nausea, vomiting)

- Edinger Westphal nucleus of III nerve is stimulated (miosis)

- Vagal centre (bradycardia)

Miosis

- Constriction of the pupils
- By stimulating Edinger Westphal nucleus of III nerve
- Miosis is a pharmacologic action to which little or no tolerance develops
- valuable in the diagnosis of opioid overdose.

Truncal Rigidity-

- Truncal rigidity reduces thoracic compliance and thus interferes with ventilation.
- Truncal rigidity may be overcome by administration of an opioid antagonist, which of course will also antagonize the analgesic action of the opioid.
- Preventing truncal rigidity while preserving analgesia requires the concomitant use of neuromuscular blocking agents.

Peripheral Effects

Cardiovascular System

- Bradycardia
  Meperidine is an exception (can result in tachycardia)
- Hypotension - due to
  -peripheral arterial and venous dilation
  -depression of vasomotor centre
  -release of histamine.
- Increased PCO_2 leads to cerebral vasodilation associated with a decrease in cerebral vascular resistance, an increase in cerebral blood flow, and an increase in intracranial pressure.

Gastrointestinal Tract

Constipation

- no tolerance
- Opioid receptors exist in high density in the gastrointestinal tract
- constipating effects of the opioids are mediated through an action on the enteric nervous system as well as the CNS
- gastric secretion of hydrochloric acid is decreased
- propulsive peristaltic waves are diminished
- tone is increased
- this delays passage of the fecal mass and allows increased absorption of water, which leads to constipation
- so used in the management of diarrhea

Biliary Tract

- sphincter of Oddi may constrict
- contract biliary smooth muscle
- result in biliary colic

Renal

- Renal function is depressed by opioids
- decreased renal plasma flow
- enhanced renal tubular sodium reabsorption
- Ureteral and bladder tone are increased
- Increased sphincter tone may precipitate urinary retention
- ureteral colic caused by a renal calculus is made worse by opioid-induced increase in ureteral tone

Uterus-

- may prolong labor
- both peripheral and central actions of the opioids can reduce uterine tone

Neuroendocrine-

- stimulate the release of ADH, prolactin, and somatotropin
- inhibit the release of luteinizing hormone

Pruritus-

- CNS effects and peripheral histamine release may be responsible for these reactions
- pruritus and occasionally urticaria (when administered parenterally)

Miscellaneous

The opioids modulate the immune system by

- lymphocyte proliferation
- antibody production
- chemotaxis

Clinical Use of Opioid Analgesics

- **Analgesia**
- **Cough**
- **Diarrhea**
- **Acute Pulmonary Edema**
- **Balanced anaesthesia**
- **Preanaesthetic medication**
- **Relief of anxiety and apprehension**

Toxicity & Undesired Effects

Behavioral restlessness, tremulousness, hyperactivity (in dysphoric reactions)
Respiratory depression
Nausea and vomiting
Increased intracranial pressure
Postural hypotension accentuated by hypovolemia
Constipation
Urinary retention
Itching around nose, urticaria (more frequent with parenteral and spinal administration)

Acute morphine poisoning

- >50 mg of morphine
- Lethal dose is 250mg
- Stupor, coma, shallow breathing, cyanosis, pinpoint pupil, fall in BP, convulsions
- Death due to respiratory failure

Treatment

- Positive pressure respiration
- Iv fluids
- Gastric lavage with potassium permagnate
- Naloxone

Tolerance and Dependence

- With frequently repeated therapeutic doses of morphine, there is a gradual loss in effectiveness
- To reproduce the original response, a larger dose must be administered
- Along with tolerance, physical dependence develops
- Physical dependence is defined as a characteristic **withdrawal** or **abstinence syndrome** when a drug is stopped or an antagonist is administered

Tolerance and Dependence

- Maintenance of normal sensitivity of receptors requires **reactivation by endocytosis and recycling**.
- activation of receptors by endogenous ligands results in endocytosis followed by resensitization and recycling of the receptor to the plasma membrane.
- But morphine fails to induce endocytosis of the -opioid receptor - tolerance and dependence.
- In contrast, methadone, used for the *treatment* of opioid tolerance and dependence, does induce receptor endocytosis.

Tolerance and Dependence

- NMDA receptor ion channel complex play a critical role in tolerance development and maintenance

- NMDA-receptor antagonists such as ketamine can block tolerance development

Withdrawal

Withdrawal is manifested by significant somatomotor and autonomic outflow-

- agitation
- hyperalgesia
- hyperthermia
- hypertension
- diarrhea
- pupillary dilation

- release of all pituitary and adrenomedullary hormones

- affective symptoms

  -dysphoria

  -anxiety

  -depression

These phenomena are highly aversive and motivate the drug recipient to make robust efforts to avoid the withdrawal state

Contraindications and Cautions in Therapy

Use of Pure Agonists with Weak Partial Agonists

- morphine with pentazocine - risk of diminishing analgesia or even inducing a state of withdrawal

Use in Patients with Head Injuries

- Carbon dioxide retention caused by respiratory depression results in cerebral vasodilation.
- In patients with elevated intracranial pressure, this may lead to lethal alterations in brain function.
- Marked respi. depression
- Vomiting, miosis, altered mentation by morphine interferes with assessment of pt condition

Use during Pregnancy

- In pregnant women who are chronically using opioids, the **fetus may become physically dependent in utero** and manifest withdrawal symptoms in the early postpartum period.

- A daily dose as small as 6 mg of heroin (or equivalent) taken by the mother can result in a mild withdrawal syndrome in the infant, and twice that much may result in severe signs and symptoms, including irritability, shrill crying, diarrhea, or even seizures.

- When withdrawal symptoms are mild - diazepam
- with more severe withdrawal - methadone

Use in Patients with Impaired Pulmonary Function

- opioid analgesics may lead to acute respiratory failure.

Use in Patients with Impaired Hepatic or Renal Function

- morphine and its congeners are metabolized primarily in the liver
- Half-life is prolonged in patients with impaired renal function

Use in Patients with Endocrine Disease

-adrenal insufficiency (Addison's disease) and hypothyroidism (myxedema) –

-prolonged and exaggerated responses to opioids.

Related drugs

Pethidine

- 1/10th in analgesic potency
- Spasmodic action on smooth muscles is less
- Tachycardia (**antimuscarinic** action)- it is related to atropine, even acts on opioid receptors
- Safer in asthmatics (less histamine release)
- Uses- analgesia, preanaesthetic medication
- Preferred opioid analgesic during labour (less neonatal respi depression)

Fentanyl

- 80-100 times more potent than morphine
- few cardiovascular effects
- little propensity to release histamine.
- Because of high lipid solubility, it enters brain rapidly and produces **peak analgesia in 5 min** after i. v. injection.
- The **duration of action is short**: starts wearing off after 30-40 min due to

  redistribution
- **Transdermal** fentanyl has become available for use in cancer

Methadone

- Slow & persistant action
- Sedative & subjective effects are less intense
- No kick
- Less abuse potential
- Use- as substitute therapy for opioid dependence
- 1mg methadone for 4 mg morphine.

Tramadol

- Analgesic action mechanism
  - Weak affinity for μ-opioid receptor
  - norepinephrine & 5-HT reuptake Inhibition
- Advantage
  - Less respiratory depression, nausea, vomiting, constipation
  - Less abuse potential
  - Rapid psychomotor recovery
- Labour pain, injury, surgery (other short lasting pain)
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

Pentazocine (κ analgesic)

- It has agonistic actions and weak opioid antagonist
- elicit dysphoric and psychotomimetic effects
- increase in blood pressure and heart rate

Uses-

- moderate to severe pain
- as a preoperative medication and
- as a supplement to anesthesia

Buprenorphine (weak μ agonist & κ antagonist)

- 25-50 times more potent than morphine
- Sublingual route
- Slower onset & longer duration of action
- Postural hypotension is marked
- Cannot be used during labour (respi dep not reversed by naloxone)

Uses-

- Long lasting pain- cancer
- Tt of morphine dependence

Naloxone (μ, κ, δ antagonist)

- Antagonizes all morphine actions
- Sedation is less completely reversed
- Blocks placebo, acupuncture, stress induced analgesia

Use

- Morphine poisoning
- Diagnostic test for opioid addiction
- Revert neonatal respi depression due to opioid use during labour

Peripherally Acting Opioid

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist
    → analgesia without CNS side effect
- Loperamide, Diphenoxylate
  - μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia
  - Relieve diarrhea
- Alvimopan
  - peri μ-opioid receptor antagonist
  - Relieves constipation in opium addicts
  - Without precipitating opioid withdrawl
  - Treat postoperative paralytic ileus

Opioid with Other Analgesics

- Goal of using analgesics in combination
  - Achieve superior analgesia
  - Reduce dose of each drug
  - Minimizing side effect
- NSAID
  - Synergistical action with systemic opioid to produce analgesia
- Local anesthetics and opioid
  - Synergistical pain relief when intrathecal or epidural administration