Opioid Pharmacology

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Some important terms

Analgesics: Are the Drugs which selectively relieve pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering the consciousness – **Opioids and NSAIDS**

Opioids: Any drug which binds to the opioid receptors (Pharmacologically related) in the CNS and antagonized by Naloxone . They may be – Natural, Synthetic and semisynthetic

Opiates: Drugs derived from opium – Natural or semisynthetic

Narcotics: Drugs derived from **opium** or opium like compounds, with **potent analgesic** effects associated with significant **alteration of mood** and behavior, and with the potential for **dependence and tolerance** following repeated administration.

Pharmacodynamics

Opioids Mechanism Of Action

produce their actions at a cellular level by activating opioid receptors. These receptors are distributed throughout (CNS), cerebral cortex, thalamus and the spinal cord.

- All receptors are G-protein coupled receptors
- Located on pre junctional neurons
- Inhibits release of transmitters – NA, DA, 5-HT, GABA and Glutamate
- Activation reduces intracellular cAMP formation -

Opening of K+ channel via μ and δ. and suppression of N type of Ca++ channels

- Ultimately **Hyperpolarization and reduced intracellular Ca++**

Reduced Neurotransmitter release

Pure opioid agonists (morphine, diamorphine,pethidine and fentanyl) bind to opioid receptors and demonstrate high intrinsic activity at the cellular level.

Partial opioid agonists (buprenorphine, pentazocine) bind to opioid receptors, but produce a sub-maximal effect compared to pure agonists and so have less intrinsic activity associated with receptor binding.

Opioid antagonists (naloxone, naltrexone), have receptor affinity but no intrinsic activity.

Opioid Receptors

Receptor		Prototypic-drug	actions
Mu	**μ1**	**Most endogenous , naturally-occurring or synthetic opioids**	**Supraspinal analgesia ,euphoria**
	μ2	**Morphine**	**Respiratory depression, anorexia, Cardiovascular effects , prolactin release, dependence, and sedation**
Delta δ		**Enkephalins**	**Spinal analgesia**
Kappa κ		**Ketocyclazocine and dynorphin**	**Spinal analgesia Sedation, miosis, dyspnea, dependence, dysphoria, and respiratory depression**
Sigma σ		**N - allylnormetazocine**	**Psycotomimetic effects** They **are no longer considered opioid receptors**, but rather the target sites for phencyclidine (PCP) and its analogs

CLASSIFICATION OF OPIOIDS

- **Traditional** based upon analgesic potency

Strong: morphine, pethidine, fentanyl, alfentanil, remifentanil,sufentanil
Intermediate: buprenorphine, pentazocine, butorphanol, nalbuphine
Weak: codeine

- **Origin**

Naturally occurring: codeine, morphine, papavarine
Semisynthetic: diamorphine, dihydrocodeine, buprenorphine
Synthetic: pethidine, fentanyl, alfentanil, methadone,

Function:

Pure agonists: morphine, fentanyl, alfentanil, remifentanil, sufentanil
Partial agonist: buprenorphine
Agonists-antagonists: pentazocine, nalbuphine, nalorphine
Pure Antagonists: naloxone, naltrexone

PHARMACOLOGI CAL ACTIONS OF OPIOID AGONISTS

-Central nervous system

Analgesia

- Most effective in relieving dull, continuous and poorly localized pain arising from deeper structures,
- Neuropathic pain can be very resistant, but patients may report that pain is still present

Sedation

- Drowsiness, feeling of heaviness and difficulty in concentrating
- Sleep may occur with relief of pain, while they are not true hypnotics.

Hallucinations

- ***Euphoria and dysphoria***

Morphine and other opioids cause a sense of contentment and well being (euphoria). If there is no pain, morphine may cause restlessness and agitation (dysphoria).

- ***Tolerance and dependence****:*

- Tolerance is the decrease in effect seen despite maintaining a given concentration of a drug. The mechanism is not fully understood but could involve down regulation of opioid receptors or decreased production of endogenous opioids.
- Dependence exists when the sudden withdrawn of an opioid, after repeated use over a prolonged period, results in various physical and psychological signs. Include; restlessness, irritability, increased salivation, lacrimation and sweating, muscle cramps, vomiting and diarrhea.

- **Cardiovascular system**

Mild bradycardia, Peripheral vasodilatation, caused by histamine release and reduced sympathetic drive may result in a slight fall in blood pressure that may be significant in hypovolaemic patients.

- **Respiratory system**

Respiratory depression, Codeine suppresses coughing to a degree similar to morphine, but has lesser analgesic activity. Also, caused bronchospasm

Gastrointestinal System

CONSTIPATION: Due to direct action on intestine reducing propulsive movement, spasm of sphincters, decrease in all GIT secretions

Stimulation of the chemoreceptor trigger zone causes nausea and vomiting

- ***Endocrine System***

The release of ACTH, prolactin and gonadotrophic hormone is **inhibited**. Secretion of ADH is **increased**.

- ***Ocular effects***

opioids resulting in constriction of the pupils (miosis).

- ***Histamine release and itching***

Some opioids cause histamine release from mast cells resulting in urticaria, itching, bronchospasm.

- ***Muscle rigidity***

Large doses of opioids may occasionally produce generalized muscle rigidity especially of thoracic wall and interfere with ventilation.

- ***Immunity***

The immune system is depressed after long-term opioid abuse.

Effects on pregnancy and neonates

• All opioids cross the placenta and if given during labour, can cause **neonatal respiratory depression**.

Chronic use by the mother may cause **physical dependence** in utero and lead to a **withdrawal reaction in the neonate at birth** that can be life threatening.**There are no known teratogenic effects**.

Pharmacokinetics

- Opioids are weak bases.
- many opioids then undergo **extensive first-pass metabolism** in the intestinal wall and liver, resulting in **low oral bioavailability**.
- High lipid solubility facilitates opioid transport into the biophase or site of action. Consequently, high lipid solubility confers a more rapid onset of action.

- Drugs with high lipid solubility, high unionized fraction or **low protein binding in the plasma**, demonstrate **large volumes** of distribution. opioids (like alfentanil, sufentanil or fentanyl) produce a short duration of action. drug rapidly redistributes from the CNS to other tissues.
- Opioids are metabolized mainly in the liver to both **active and inactive compounds** that are excreted in urine and bile. Morphine and other opioids are excreted partly in the bile as water-soluble glucuronides.

- **Morphine**
- Morphine is a naturally occurring phenanthrene derivative. It is the standard drug against which all other opioids are compared.
- Morphine can be given orally, intramuscularly (IM), intravenously(IV), subcutaneously (SC), rectally, epidurally and intrathecally.

• **Morphine is extensively metabolized by the gut wall** and the liver to morphine-3-glucuronide (70%), morphine-6 glucuronide (10%) and to sulphate conjugates. morphine-6 glucuronide more potent than morphine and is normally excreted in urine.

• Neonates are more sensitive than adults to morphine due to reduced hepatic conjugating capacity.

• In the elderly, owing to reduced volume of distribution, peak plasma level of morphine is higher compared to younger

Pharmacological action

a. **Analgesia:** relief of pain without the loss of consciousness by raising the **pain threshold** at the spinal cord level and, more importantly, by altering the **brain's perception of pain**.

b. **Euphoria:** a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmental area.

c. **Respiration:** respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. Tolerance to this effect does develop quickly with repeated dosing, which allows the safe use of *morphine* for the treatment of pain when the dose is correctly titrated

d. **Depression of cough reflex:** Both *morphine* and *codeine* have antitussive properties.

e. **Miosis:** The **pinpoint pupil** characteristic of *morphine* use results from stimulation of μ and κ receptors. There is little tolerance to the effect, and all *morphine* abusers demonstrate pinpoint pupils. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.

. Emesis: directly stimulates the chemoreceptor trigger zone and causes vomiting. *Morphine* can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter.

h. Cardiovascular: has no major effects at lower dosages. With large doses, hypotension and bradycardia may occur; because of carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid pressure

i. Histamine release: causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, *morphine* should be used with caution in patients with asthma

j. Hormonal actions: increases **growth hormone** release and enhances **prolactin secretion**. It increases **antidiuretic hormone** and leads to urinary retention.

k. Labor: may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions.

Therapeutic uses

- Analgesic:Long Bone Fracture, Myocardial Infarction,Terminal stages of cancer, Burn patients, Postoperative patients, Visceral pains – pulmonary embolism, pleurisy, acute pericarditis, Biliary colic and renal colic, **Obstetric analgesia**

Diarrhoea – colostomy - Loperamide,Diphenoxylate

Adverse Effects

- Respiratory Depression: Infant and Old
- Vomiting
- Sedation, Mental Clouding – sometimes dysphoria
- Hypotensive effect
- Rise in Intracranial Pressure
- Apnoea: Newborn
- Urinary retention
- Idiosyncrasy and allergy
- Acute Morphine Poisoning: occurs if >50 mg (Lethal dose – 250 mg), Gastric lavage with KMNO4, Specific antidote: Naloxone: 0.4 to 0.8 mg IV repeatedly in 2-3 minutes till respiration picks up
- Tolerance and dependence

Codeine

is a naturally occurring opioid that is a **weak analgesic** compared to *morphine*. It should be used only for mild to moderate pain. *codeine* has been replaced by drugs such as *dextromethorphan*, a synthetic cough depressant that has relatively no analgesic action and a relatively low potential for abuse in usual antitussive doses

Oxycodone

is a semisynthetic derivative of *morphine*. It is orally active

Oxymorphone

When given parenterally it is approximately ten times more potent than *morphine*

Hydromorphone and hydrocodone
are orally active, **semisynthetic analogs of *morphine* and *codeine*, respectively.**
Oral *hydromorphone* is approximately more potent than *morphine*.
It is preferred over *morphine* in patients with renal dysfunction due to less accumulation of active metabolites.
Hydrocodone is the methyl ether of *hydromorphone*, but is a weaker analgesic than *hydromorphone*, with oral analgesic efficacy comparable to that of morphine
It is also used as an antitussive and to treat moderate to severe pain.

Meperidine

–is a lower-potency synthetic opioid structurally unrelated to *morphine*. 1/10th as potent as Morphine, but Efficacy is similar

– Produces as much sedation, euphoria and respiratory depression in equi analgesic dose and similar abuse potential than morphine

– Less spasmodic action in smooth muscles – less miosis, constipation and urinary retention(has anticholinergic effects).

-very lipophilic and, resulting in an increased incidence of delirium as compared to other opioids.

– Rapid but short duration of action (2-3 Hrs)

–**Tachycardia**

– **Devoid of antitussive action**

– **safer in asthmatics,** Less histamine release than morphine.

Meperidine: Metabolized in liver – mepiridinic acid and norpethidine.

Adverse Effects:

• Similar to Morphine

• Atropine like effects – dry mouth, blurred vision, tachycardia

Normeperidine has significant neurotoxic actions that can lead to delirium, hyperreflexia, and possibly seizures

• Overdose – tremors, **mydriasis**, delirium and convulsion due

Meperidine should not be used in elderly patients or those with renal insufficiency, hepatic insufficiency,

•Uses:

• Analgesic as substitute of Morphine

• Pre anaesthetic medication

• As analgesic during labour – less fetal respiratory depression than morphine

Methadone

Chemically dissimilar but similar in most of pharmacological actions – analgesic, respiratory depression etc.

Used **as substitution therapy as opioid dependence**: 1:4mg and 1:20 mg of Morphine and Pethidine respectively

• Codeine is used as substitution in **Methadone addiction**

Tramadol

Centrally acting analgesic

• **Very low action on opioid receptors**

Other mechanisms involved in analgesic action – **5-HT and NA reuptake inhibition** – spinal inhibition of pain

Only Partially reversed by **Naloxone**

Used in chronic **neuropathic pain** and short **diagnostic procedures**

Fentanyl

a synthetic opioid chemically related to *meperidine*, has 100-fold the analgesic potency of *morphine* and is **used for anesthesia**.

The drug is highly lipophilic and has a **rapid onset** and **short duration** of action (15 to 30 minutes).

Fentanyl is metabolized to **inactive metabolites,** *Fentanyl* is combined with local anesthetics to provide **epidural analgesia** for labor and postoperative pain.

IV *fentanyl* is used in anesthesia for its analgesic and sedative effects.

An oral transmucosal preparation and a transdermal patch are also available

Sufentanil , ***alfentanil*** , and ***remifentanil***
are three **synthetic opioid agonists** related to *fentanyl*. They differ in potency and metabolic disposition.
Sufentanil is even more potent than *fentanyl*, while the other two are less potent and shorter acting.
These agents are mainly used for their analgesic and sedative properties during surgical procedures requiring anesthesia.
Buprenorphine
is classified as a **partial agonist, acting at the μ receptor**
it can also precipitate withdrawal in users of *morphine* or full opioid agonists. Used is in **opioid detoxification**, because it has shorter and less severe withdrawal symptoms compared to *methadone*
Adverse effects: **respiratory depression** that cannot easily be reversed by ***naloxone*** **and decreased**

***pentazocine* ,Nalbuphine and butorphanol:** are mixed opioid agonist–antagonists. They play a limited role in the treatment of chronic pain

Butorphanol

is available in a nasal formulation that has been used for severe headaches, but has also been associated with abuse.

Naloxone

- **Competitive antagonist of all types of opioid receptors**
- But, blocks μ-receptors at much lower dose. Always injected IV (0.4 t0 0.8 mg) - All symptoms of Morphine action are antagonized – respiratory stimulation

Uses:

- Acute Morphine Poisoning
- New Born – opioid poisoning
- Reverse respiratory depression intra operatively
- Diagnosis of Morphine addiction
- Alcohol intoxication