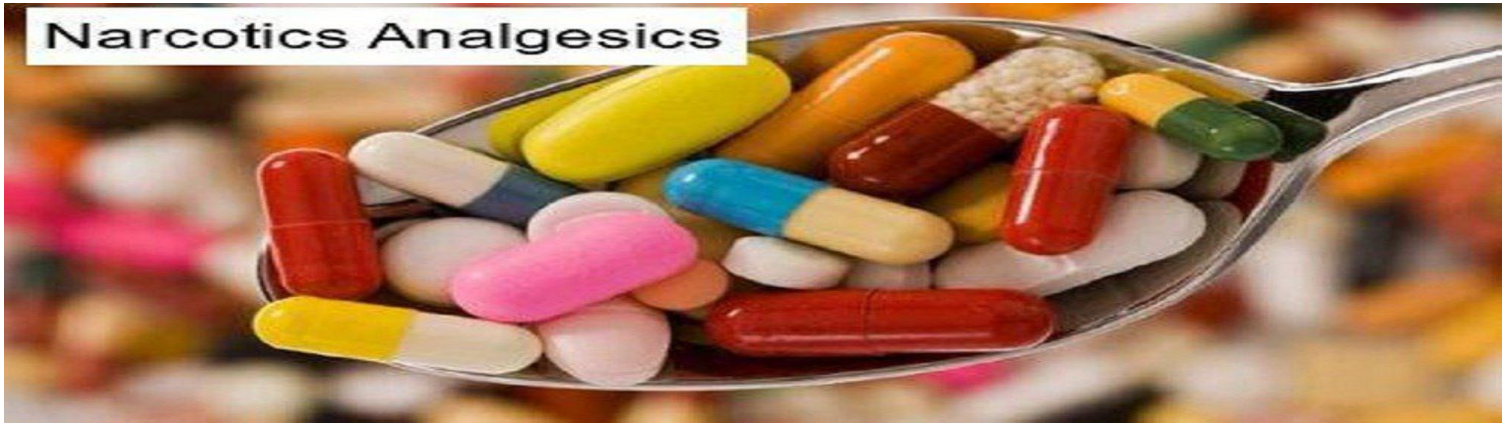


Narcotic Analgesics

د.اسماء الثويني

Asist.Prof./M.B.Ch.B/M.S.C/P.h.D

Pharmacology and therapeutics

- ***Analgesic:*** Is the drug that relieves pain, they are divided into two types:
- Narcotic: which act centrally as Opioids.
- Non-narcotic: they act peripherally as Aspirin.
- ***Narcotics:*** they relieve pain and also cause drowsiness and sedation. The prototype drug is (Morphine).
- **Opioids receptors:**
- **4 families** of receptors which are: **murra, kappa, delta, and sigma.** Each of these receptors exhibit different specificity for the drug that they bind.

- **Mode of action:**
- All opioids receptors are coupled to **inhibitory G-protein** **so they decrease cAMP level and cause cellular hyperpolarization.**
- **Distribution of opioid receptors:**
- **CNS (Brain stem, Thalamus, Hypothalamus, Limbic System and Spinal cord)**
- They are also found in the **periphery** (**like GIT**) and in the **Immune cells**

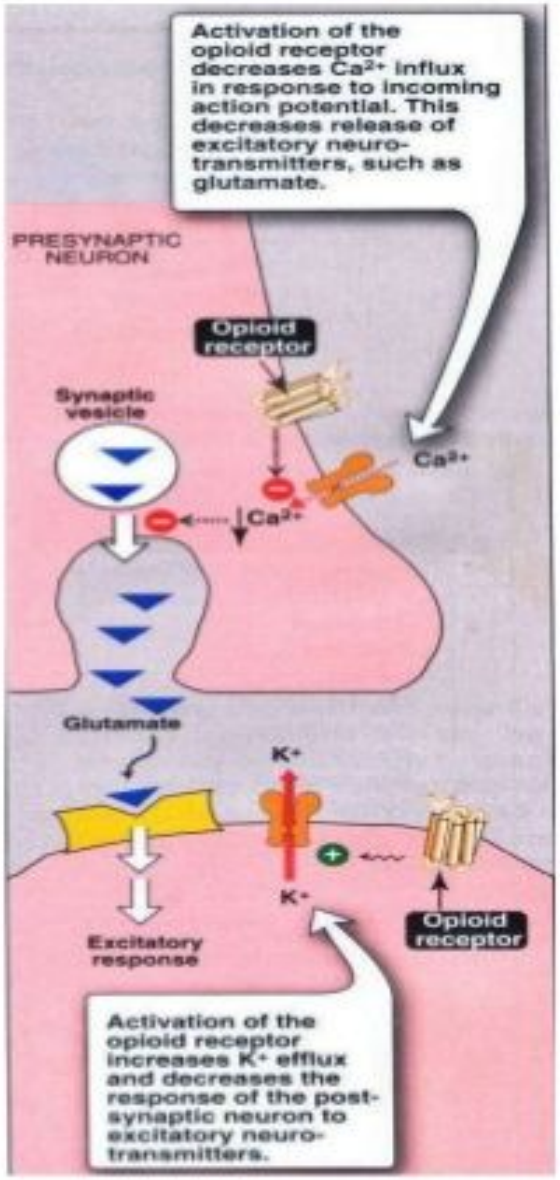
Mechanism of Action

All opioid receptors are G-protein coupled receptors and inhibit adenylate cyclase.

They are also involved in

- Postsynaptic hyperpolarization (increasing K+ efflux)
- Reducing presynaptic Ca^{++} influx

thus inhibits neuronal activity.



- **Classification of Opioids:**
-
- **a. Strong agonists:**
  - ***Morphine***
  - ***Meperidine (Pethidine)***
  - ***Methadone***
  - ***Fentanyl***
  - ***Heroin (Diamorphine)***
- **b. Moderate agonists:**
  - ***Codeine***
  - ***Dextropropoxyphene***
  - ***Diphenoxylate***
  - ***Loperamide***
  - ***Dextromethorphan***
- **d. Partial agonist:**
  - ***Pentazocine***
  - ***Phenazocine***
- **d. Antagonists:**
  - ***Naloxone***
  - ***Naltrexone***
  - ***Nalorphine***
  - ***Nalmefene***

• Morphine

- **Pharmacological effects:**
- **1. On CNS:**
- ***Depressant, stimulant, euphoria, dysphoria & dependence.***
- ***A .Depressant actions:***
- **1. Analgesia: (sensory and emotional) pain is felt but the sensation is not more unpleasant.**
- **2. Drowsiness and mental clouding,** so it has useful hypnotic and tranquilizer effect.
- **3. Respiratory effect: (inhibition of respiratory center)**decrease the rate and depth by **decreasing the sensitivity of the respiratory center to raised CO_2 tension** in the blood (over dose respiratory arrest).
- Morphine is dangerous in patients with **chronic obstructive pulmonary disease ,and asthma** ,in which it will also **increase the viscosity of bronchial secretions** in addition to **bronchospasm due to histamine release.**
- **4. Inhibition of cough center:** cough suppression.

- **5. Increase the intracranial pressure:** due to CO_2 retention, dilation of cerebral vessels, and increase the CSF pressure, therefore **morphine is contraindicated in patients with severe head injury.**

- ***B. Stimulatory actions:***
- **1. Miosis:** pin point pupil is characteristic of morphine poisoning and addicts and occur as a result of stimulation of **mu and kappa receptors**. Morphine **stimulates 3rd nerve nucleus** which cause enhancement of the parasympathetic stimulation to the eye and thus miosis. ***Even addicts show pin point pupil,*** This is an important diagnostic feature of coma because most other causes of coma cause dilation of the pupil.
- **2. Emesis:** 40% nausea and 10% vomiting, this is caused by direct stimulation to the chemoreceptor trigger zone.
-
- **2. peripherally >>>>>On Smooth Muscles: (spasmogenic agent)**
- **a. GIT : stim. of mu and delta R. in entric N.S.**
- ***In the small intestine***, **decreases motility** and causes **spasm of sphincters**.
- ***In the large intestine***, it **decreases peristalsis**. It also **decreases intestinal secretions**.
- ***In the stomach***, it **delays gastric emptying**, **decreases motility** and **HCl secretion**.
- It causes **constipation** and **increases the intrasigmoidal pressure**, therefore it is contraindicated in patients with **diverticular disease** (Pethidine does not produce this high pressure and it can be used if needed).

- **b. Biliary system :**
- ***Spasm of sphincter of oddi*** ⍰ increases intrabiliary pressure. Sometimes, **biliary colic is worsened by morphine**. **This effect can be reversed by Naloxone or GTN**
- **c. The bronchi :** they are constricted (i.e. spasm).(vagal st.) and cause release of histamine.
- **d. Ureter :**spasm.
- **e. Bladder:** spasm of the sphincter that leads to retention of urine in patients with benign prostatic hyperplasia.
- **f. Uterus:** **labor is prolonged** due to slowing of the effective contraction and spasm in cervical sphincter.
- **g. CVS:**

•In the normal persons the effects on CVS are not so important, but can benefit patients with ***acute left ventricular failure (acute pulmonary edema)*** due to the following effects:

•***Relieve mental distress*** (affect emotional pain)⍰ by tranquilizer effect.

•***Relieve cardiac distress***

•***Relieve respiratory distress*** ⍰ by rendering the respiratory center insensitive to stimuli coming from the congested lungs.

•Decrease blood pressure and bradycardia.(vag.stim.)

- **Pharmacokinetics:**
  - **Absorption** from GIT is **slow**.
  - It undergoes **significant 1st pass elimination**, therefore it is usually given **i.m. or i.v. or s.c.**, also given in buccal and sublingual routes in which the dose is equal to that of the i.m. route, and it is given as transdermal patch.
  - It is also taken by **inhalation** of crude opioid for the non-medical purposes rapid onset of action.
  - Morphine enters all tissues and can cross the **placenta** causing **respiratory depression in the fetus** at birth.
  - **$t_{1/2}$ = 2 hrs, duration of action = 4 - 6 hrs.**
  - It is metabolized in liver and kidney to the followings:
    - **Morphine-6-glucoronide active**
    - **Morphine-3-glucoronide inactive**
  - Conjugated morphine is excreted in urine and small amount appears in the bile.

- **Clinical Uses:**

1. **Relief of severe pain**, which is either visceral (MI)or somatic (as wounds, fractures). (distinguish between morphine and aspirin is used only in mild and moderate somatic pains).
2. **Relief of anxiety in serious and frightening diseases** e.g. accidents or hemorrhage (in this case morphine should be given after replacement of fluid loss).
3. **Relief of dyspnea in acute left ventricular failure (pulmonary oedema)**.
4. Production of **euphoria**.(non medical use)
5. adjunct to anesthesia to decrease post operative pain.
6. Symptomatic control of non-serious **diarrhea** e.g. travelers diarrhea (codeine & loperamide are preferred)
7. Suppression of **cough** (codeine preferred).

- **Adverse Effects :**

1. **Respiratory depression.**
2. **Vomiting.**
3. **Dysphoria.**
4. **Hypotension.**
5. **Retention of urine in (BPH).**
6. **Pruritis (itching around the nose).**

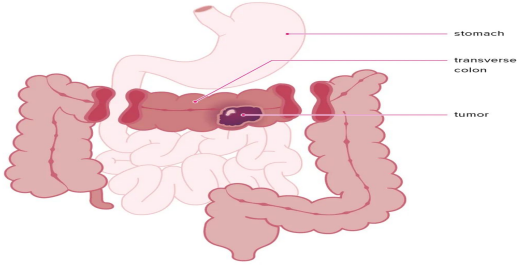
- **Contraindications:**

1. **CNS:**

   Head injury because it increases intracranial pressure.

2. **GIT :**
   a. **Diverticulitis**
   b. **Biliary infections .**
   c. **Intestinal anastamosis and ob**

3. **Respiratory system:** Asthma & COPD.



- **4. Avoided during labor.**
- **5. inferior MI (hypotension and brady**
-

- **Tolerance & dependence(addiction):**
- There is **cross tolerance** between opioids and other CNS depressants as barbiturates & alcohol.

- **Treatment of addicts: (chronic use)**
  1. **Withdraw morphine gradually**.
  2. Substitute with **methadone** which produces mild withdrawal syndrome, since it has **long $t_{1/2}$ (48 hrs)**, then substitute with benzodiazepine as diazepam.
  3. **Clonidine** decreases the severity of withdrawal syndrome by decreasing the effects of noradrenaline hyperactivity.
  4. Sometimes, we also use **β-blockers as propranolol** that control sympathetic over activity of withdrawal.
-
- **Morphine poisoning: (acute toxicity) due to high dose.**
- **Coma, slow & shallow respiration, pinpoint pupil**, & cyanosis occurs.
- The main signs of morphine poisoning are:

1. Respiratory depression.
2. Coma with constricted pupils (miosis), while in most other cases of coma the pupil is dilated.

-
- ***Treatment of morphine poisoning :***

1. **Support respiration & circulation** till antagonize the effect of opioids.
2. Give **Naloxone** i.v. (its action lasts for 1 hr.) it's a pure opioid antagonist.

• Individual opioids

A. high efficacy opioids:

- 1. Morphine 2. Pethidine 3. Methadone 4. Fentanyl 5. Diamorphine.

- **Pethidine (meperidine):**
- It is **commonly used**, has **less efficacy than morphine**, but it's pain control beyond reached of codeine. It is **like morphine** in **causing respiratory depression, euphoria & vomiting**. **Structurally, it is not related to morphine, but it shares many properties** with morphine including that of being **antagonized by Naloxone**.
- Pethidine ***$t_{1/2}$*** **is 3 hrs**, usually given as injection (bioav. Is 50%)
- ***Pethidine differs from morphine by:***

1. Doesn't suppress **cough** usefully.
2. Causes less intense & less frequent **constipation**.
3. Less increase in **intrasigmoidal and intrabiliary pressure**
4. It less likely to prolong child-birth so is **used in 1st stage of labor.**
5. In overdose pethidine **can't produce pin-point pupil** because of atropine like effect.
6. **Dependence is less** marked than morphine.

- ***Clinical uses of pethidine:***

1. Relive **severe pain** like post-operative pain.
2. **Pre-operative** medication.
3. **1st stage of labor**

- **Methadone:**

- **structurally related to morphine**
- **very effective orally**.
- It causes **less sedation** and **less euphoria** than morphine.
- ***t1/2*** is 48 hrs.
- **Analgesia lasts for 24 hrs.**
- Dependence occurs, but is less sever and causes **less sever withdrawal syndrome** because of long $t_{1/2}$, therefore the addicts on morphine are shifted to methadone as one step of treatment.

- ***Main uses:*** **analgesia**, **cough suppression**, **treatment of opioids dependence** (morphine & heroin).
-

- **Diamorphine (heroin):**

- A semi synthetic drug made by acetylation of morphine. It is the **most powerful of all dependence producing drugs**.

- **Fentanyl:** used in general anesthesia.

A. *low to moderate efficacy opioids:*

- **Codeine:**
- **$t_{1/2}$ is 3 hrs. It is methyl morphine**, **naturally occurring** low to moderate efficacy opioids. In the body only 10% is converted to morphine, so its **action is 1/10 that of morphine** (in same conc. of both). **It lacks efficacy in severe pain**. It is used in **cough suppression** & for short term systemic **control of the acute diarrhea**. It is usually **combined with aspirin or paracetamol**.

- **Dextropropoxyphene:**
- **$t_{1/2}$ is 12 hrs. Analgesic effectiveness is equal to that of codeine**. It is less dependence-producing & less analgesic when compared to methadone. It is rapidly absorbed & metabolized in liver. In overdose it causes respiratory depression & arrhythmia because of the quinidine-like action on the heart. **Combined with aspirin & paracetamol for greater analgesic effect.**
- **Diphenoxylate & Loperamide used as antidiarrheal**
- **Dextromethorphan used as cough suppressant**

- **Tramadol:**
- **$t_{1/2}$ is 6 hrs.** It binds to **μ receptors** causing analgesia.
- . As effective as pethidine for post-operative pain & less likely to cause constipation & **less addiction & respiratory depression**. It **may cause convulsions, hallucinations** & probably anaphylaxis.
- ***D . Opioid antagonists:***

1. Naloxone:

- **Pure competitive antagonist** that antagonizes **both agonists & partial agonists**.
  - Used in the **treatment of opioid overdose**. It is **given i.v.** only because of its high pre-systemic metabolism.
    - When given i.v., it **reverses opioid-induced respiratory depression within 1-2 min** & the **duration of action is 1hr**.

.

  - Because opioid analgesic acts much longer than this (1hr), **repeated i.v. doses of Naloxone are required (or i.v. infusion)** because the patient may recover after a single dose of Naloxone & appears normal only to relapse into coma after 1-2 hrs. Response is shown by changes in respiratory rate, pupil (disappearance of miosis) & improvement of consciousness.

- ***Other use:***
-
  - Diagnosis of opioids overdose (reversal of coma)
  - to counter the excess effect of opioids **after surgical anesthesia** & **after child birth** (given to the baby).

- **2. Naltrexone:**
- It is similar to Naloxone but **longer action** ($t_{1/2}$ is 4hrs).
- Duration of action 2-3 days because the active metabolites have $t_{1/2}$ of 13 hrs.
- Advantage on Naloxone that it can be given **orally.**
- It is also used to **decrease craving for alcohol** in chronic alcoholics.
-
- **3. Nalorphine:**
- Antagonist for all effects of morphine & other opioids.
- **4. Nalmefene:**
- **I**t is the newest of all these antagonists. It is a **derivative of Naltrexone** but given **only i.v.** It has a **longer $t_{1/2}$ than Naloxone**