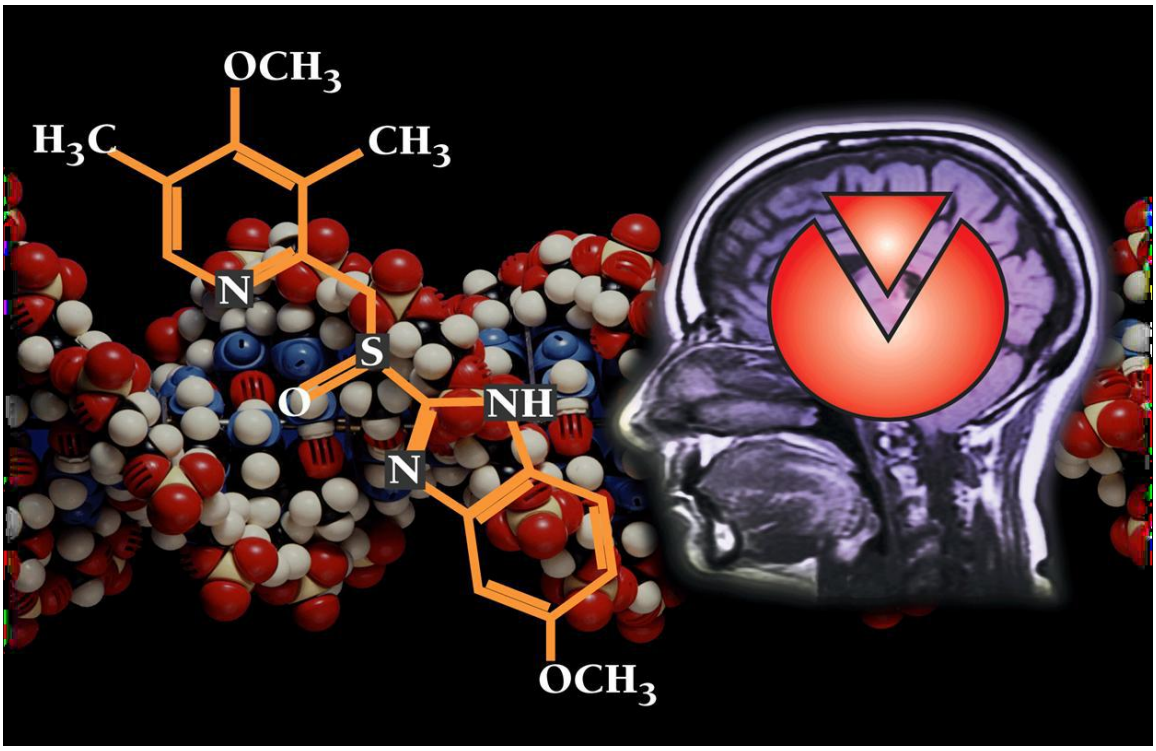
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Drugs in Management of Pain



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- Analgesics-

What are Analgesics?

- They are drugs used to induce analgesia (A state in which a painful stimuli is modulated; though perceived but felt no more painful)

Treatment of pain:-

- Nociceptive pain (stimulated by damage of any tissue):
  - NSAIDs
  - OPIOIDS
  - Adjunctive

- Neuropathic pain as cancer pain(stimulated by damage of nervous tissue):
  - NSAIDs
  - OPIOIDS
  - Adjunctive

NSAIDs: Are used for mild to moderate dull aching (it's rarely used for visceral pain).

OPIOIDS: Are used for moderate to severe pain especially for visceral pain.

- Functions mediated by endogenous **OPIOID RECEPTORS**:

- μ → **Supraspinal analgesia**, respiratory depression, euphoria, physical dependence
- δ →**Spinal analgesia**, respiratory depression, decrease GIT motility (constipation)
- K →**Spinal analgesia**, sedation, pupil constriction, dysphoria

All of them typical G-protein coupled receptors

MOA:

It performs its action by one of three ways:

Pain gate of dorsal horn

By decreasing the excitation of peripheral nociceptive afferent neuron (e.g. decrease the release of substance P)

Prequaductal gray matter

Decrease the firing level of nociceptive pathways converging at Periaqueductal GM to allow for inhibitory firing along the descending pathway returning to dorsal horn

- In other words: The periaqueductal GM will reduce the excitatory impulses that descend to dorsal horn→↓Pain

Nerve ending (pre &postsynaptic)

- Binding to **<u>presynaptic</u>** opioid receptors coupled to Gi (inhibitory G protein in G protein coupled receptor) will decrease AC (adenylyl cyclase) & cAMP → ↓voltage-gated Ca2+ channels→(no Ca^{2+} influx which is necessary for excitatory transmitter efflux) thus impeding neuronal firing

- Binding to **<u>postsynaptic</u>** opening of K channels→ so there will be <u>hyperpolarization</u> → ↓neuronal excitability

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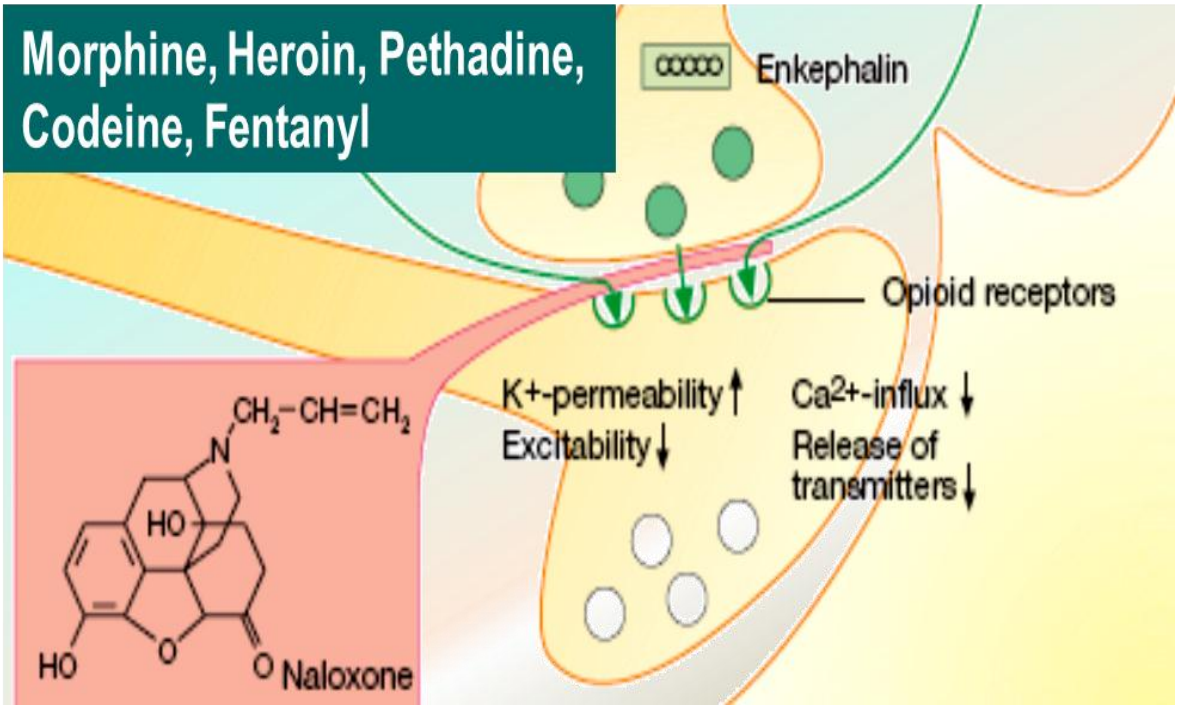


1] Morphine:-

Pharmacodynamic Actions of **Morphine** :

1. Analgesia [in acute & chronic pain]
2. Euphoria induce a powerful sense of contentment and well being
3. Respiratory depression(dyspnea "shallow breath")→⇧Pco2, this occur with high doses usually.
4. Depression of cough reflexes (antitussive action)
5. Nausea & vomiting by stimulation of the CRTZ (chemoreceptor trigger zone)
6. Pinpoint pupil (meiosis):- characteristic of morphine use due to stimulation of (Edinger-Westphal nucleus) of the occulomotor nerve by μ, κ effects, which causes enhanced parasympathetic stimulation of the eye, (this is very important diagnostically. When a patient present with respiratory depression and pinpoint pupil we immediately know that he took morphine)

7. Effects on GIT: increase in tone and decrease in motility →severe constipation (so we can use this drug to relieves diarrhea)
8. ↑ pressure in the biliary tract and constriction of biliary sphincter because of the contraction of gall bladder and the ureter (so we avoid using this drug with pt who suffer from renal or biliary colic)
9. Releases histamine from mast cells causing Urticaria, sweating and vasodilation and bronchoconstriction (asthmatic pt shouldn't receive the drug)
10. Decrease LH, FSH, ACTH , testosterone
    Increase Prolactin, GH, ADH → urine retention (this occur usually with chronic usage)
    (Because of these hormonal changes we don't use it with pt who has Endocrine diseases such as myxedema & adrenal insufficiency)

FSH=follicle stimulating hormone

ADH=antidiuretic hormone

ACTH=adrenal corticotropic hormone

LH=Luteinizing hormone

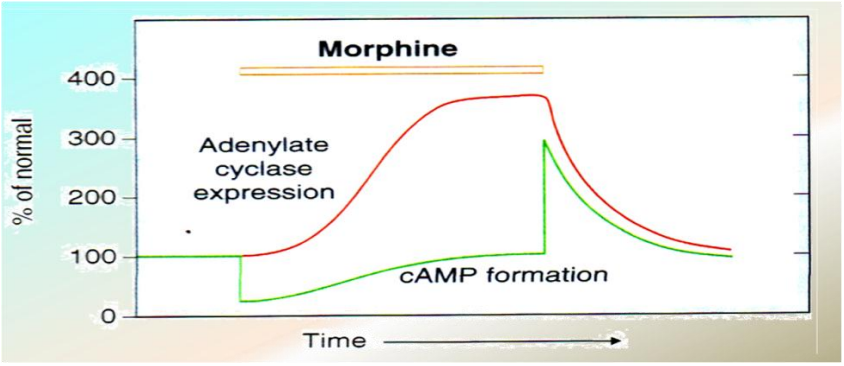
GH: growth hormone

TOLERANCE & DEPENDENCE

- Develop rapidly (tolerance to the respiratory depressant, analgesic, euphoric and sedative affect of morphine. However it doesn't develop to the pupil-constricting and constipating effect of the drug)

- Withdrawal manifestations develop upon stoppage.
- Dependence comprises both:

- **Physical dependence**(can be treated in short time)lasting for a few days in form of ↑ body ache, insomnia, diarrhea, goose flesh, lacrimation ,sweating and **pupil dilation(Mydriasis)** (these are some of the **withdrawal manifestation)**
- **Psychological dependence**(needs more time) lasting for months / years → craving (pt may come back to use this drug after his/her stoppage)



AC= Adenylate Cyclase

Note: Prolonged morphine use continuously activates Gi tending to suppress AC. The body adaptive mechanisms tend to overcome that by causing increased expression of AC. If morphine is suddenly stopped the existing excessively expressed AC in absence of morphine block will cause the withdrawal symptom. The symptoms will subside when AC expression becomes downregulated to normal levels.

Pharmacokinetics of Morphine:-

- t ½ is 2-3h .
- It is slowly & erratically absorbed orally. Medically given by IM or IV injection. It should be repeated if sustained effect is needed. (Because it has short half life)
- Undergoes enterohepatic recycling.
- Crosses BBB(so it may cause respiratory depression specially with high doses)
- Crosses placenta. (not given to pregnant women because it may cause depression for the baby)

Clinical Indications of Morphine:-

- **Control of pain**; cancer pain, severe burns, trauma
- Severe visceral pain but not renal/biliary colics and acute pancreatitis (it cause constipation and it increase pressure in the biliary tract and constriction of biliary sphincter, and it cause urine retention)
- **Diarrhea** (morphine decrease the motility and increase the tone e.g. Loperamide)
- **Cough** (e.g. Codein)
- **Acute Pulmonary oedema** (IV morphine used to relieve the pain associated with dyspnea caused by pulmonary edema associated with left ventricular failure - possibly by vasodilatory effect)
- **Myocardial Ischemia**
- **Non-painful conditions**; Heart Failure to relieve distress
- **Preanesthetic medication** (narcotic analgesic)

Adverse effects of Morphine:-

- Sedation.
- Respiratory depression.(usually in high dose)
- Constipation.
- Nausea & vomiting.
- Itching → histamine release(avoid it with asthmatic pt)
- Tolerance; not to meiosis, convulsion or constipation.
- Dependence.
- Euphoria.

Contraindications of Morphine:-

- Head injury.(Morphine causes increased cerebrospinal fluid pressure secondary to dilation of cerebral vasculature)
- Pregnancy.
- Impaired pulmonary function (means BRONCHIAL ASTHMA)
- Liver & Kidney diseases (including renal& biliary colics)
- Endocrine diseases (myxedema & adrenal insufficiency) because this drug will make hormonal changes so we can't use it in some endocrine diseases.
- Elderly → because they are more sensitive(decrease metabolism, low lean body mass & renal function) so they may develop toxicity in the normal dose !!
- Not given to infants, neonates or during child birth because the conjugating capacity is decreased(the enzymes involved in the metabolism are not developed well) so the drug will accumulate leading to respiratory depression.
- With MAOIs (Monoamine oxidase inhibitors)

2] Codeine:-

- μ Agonist
- Dependence < morphine
- Used in mild& moderate pain, cough, diarrhea

3] Heroin:-

- μ agonist
- Crosses BBB
- Converted to morphine
- **No** medical use
- Strong addicting drug

4] Meperidine - Pethidine:-

- Synthetic > effective **k** agonism

Action:-

- ↓analgesic, ↓ constipating , ↓ depressant on fetal respiration than morphine ((it is better than morphine because it is less respiratory depressive and constricting to smooth muscle (no biliary or renal colics)
- Has atropine –like action / Smooth muscle relaxant (so we like to use it as preanasthatic medication)
- No cough suppressant effect.

Indications:-

- As in morphine But not in cough & diarrhea
- Used in severe visceral pain; renal & biliary colics **sm. relaxants**) 1st choice in those pt and this effect is due to its atropine-like action
- Used in obstetric analgesia (No ↓ resp.)
- Preanaesthetic medication (better) than morphine because it has atropine like action ,(and we can use it as postanaesthetic medication also)

Side Effects:-

- Tremors, Convulsions, Hyperthermia, Hypotension
- Blurred vision, Dry mouth, Urine retention (atropine SE)
- Tolerance & Addiction

5] Tramadol:-

Synthetic, m agonist, ↓ potent, ↓ NE & 5HT also

Can be given orally; ↑ oral bioavailability → use in dentistry (teeth extraction)

Indication:-

Mild - Moderate acute & chronic visceral pain & during labor (but Pethidine is better as analgesic during labor)

Adverse effects:- (Just like the general opioids)

- Seizures (not in epileptics), Nausea , Dry mouth, Dizziness , Sedation
- Less adverse effects on respiratory & C.V.S.

6] Fentanyl:-

Synthetic, mu agonism, more potent in analgesia than meperdine & morphine

- Commonest analgesic supplement during anesthesia, IV or intrathecal. (Through the theca of the spinal cord into the subarachnoid space)

- To induce & maintain anesthesia in poor-risk patients [stabilize heart] in minor surgeries as such for those pt instead of other analgesics which are strong for them

NOTE:

It's used to induce anesthesia during the surgery!!

- In combination with droperidol as NEUROLEPTANALGESIA (diagnostic process in certain diseases / psychiatric diseases)

- In cancer pain (in its terminal stage , because we don't care about the addiction as caring about stopping the pain) & severe postoperative pain we give it as transdermal patch changed every 72 hrs.

Note: This drug is suitable as analgesic or anesthetic to cardiac old pt because it has less cardiac ADRs

Adverse effects:-

- Mimic opioid agonists
- respiratory depression and CV effects(but they are less).
- Bradycardia may still occur

7] Methadone:- *(imp)*

- Synthetic, μ- Weaker Agonist, t½ 55 h.
- Used to treat opioid (morphine as such) withdrawal :
- so given to patients during stoppage of morphine to prevent withdrawal manifestation or if withdrawal manifestation happens if addicts cannot find morphine.

- Firm occupancy of opioid receptors by methadone ↓ desire for other opioid intake, because it is producing a ↓ effect that stops withdrawal manifestations. With time addicts improve → ↓ craving

Explanation:

In an addicted pt when we want to withdrawal a certain drug (e.g. Morphine) we give them another drug from the same family but has a weaker action and longer duration (eg: Methadone) it will block the receptors so the pt will not feel any withdrawal manifestations →in each time we reduce the dosage of methadone until we withdrawal the other drug also)

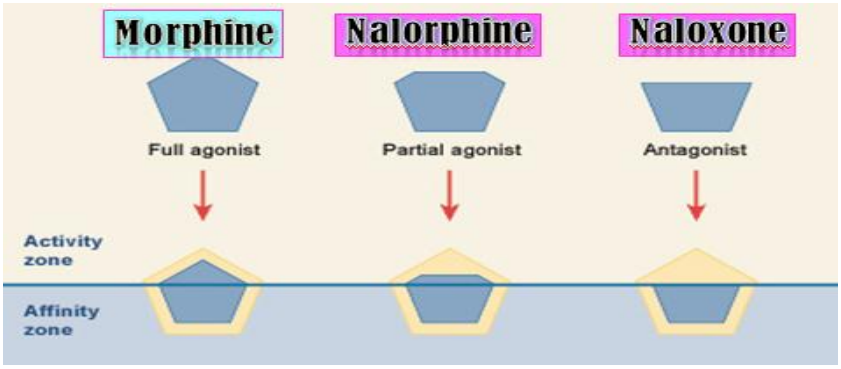
Important points:

** In non addicts, it causes tolerance & dependence but not as severe as that of morphine

** In addicted patient we use it to treat withdrawal symptoms imp

Antagonizing Acute Opioid Toxicity : *(imp)*

Acute opioid toxicity may result from clinical overdosage , so to treat this toxicity we give an antagonist not agonist as previous case



8] Naloxone:-

- Pure opioid antagonist.

- Used to treat respiratory depression caused by opioid overdose & to reverse the effect of analgesia on the respiration of the **new born baby**

- Effect lasts only for 2-4 hours.

- Precipitates withdrawal syndrome in addicts (that's mean if we give Naloxone to addicted person to opioid there will be withdrawal manifestations) imp

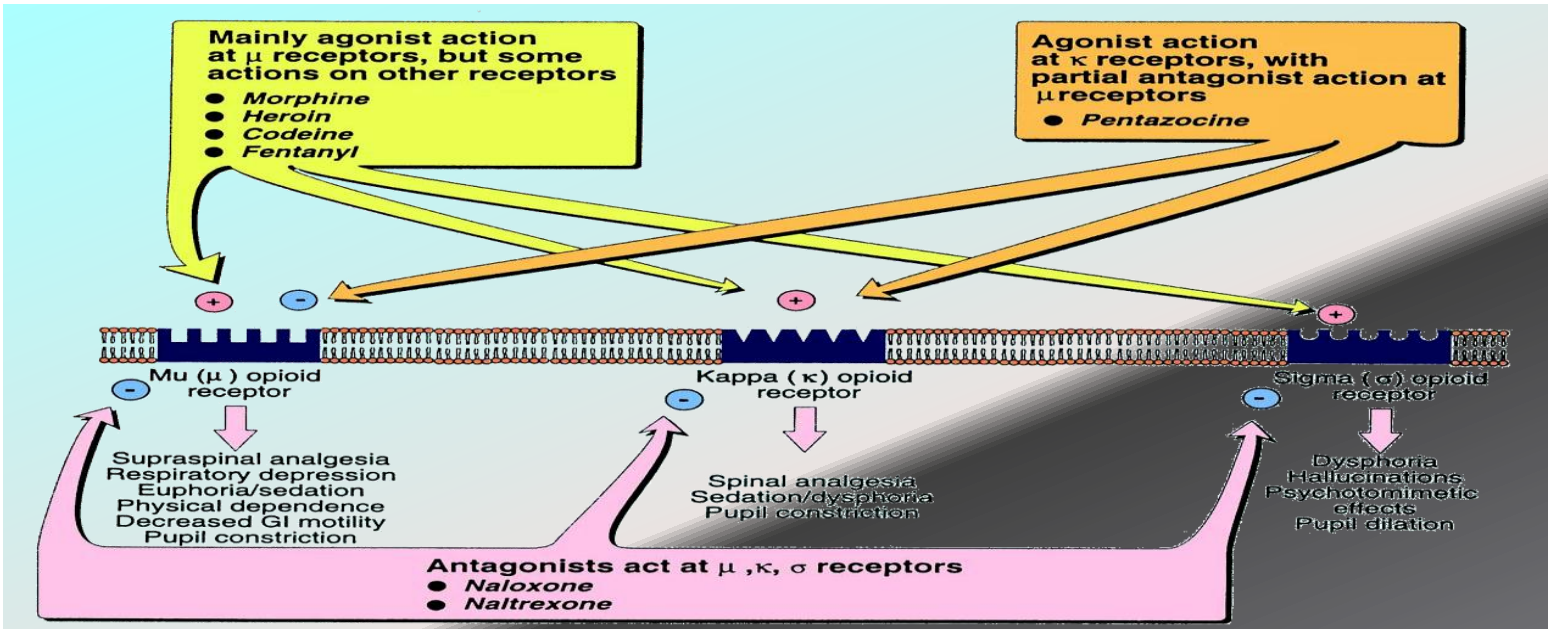
9] Naltrexone:-

Very similar to naloxone but with longer duration of action [t½=10h]

Note. You have to differentiate between: (Imp)

- If the patient is addicted and he took NALAXONE he will develop withdrawal manifestations
  ⇨ never use opioid antagonist to addicted patient

- If the patient got respiratory depression caused by morphine toxicity we use antagonist such as NALOXONE as a treatment.



N.B:

- Morphine causes Analgesia,Euphoria.,Respiratory depression,Depression of cough reflexes.,Nausea & vomiting ,Pinpoint pupil (meiosis),constipation.,↑ Pressure in the biliary tract and constriction of biliary sphincter.,Releases histamine ,Decrease LH, FSH, ACTH , testosterone,and anIncrease Prolactin, GH, ADH .
- Morphine is contraindicated with Head injury,Pregnancy,impaired pulmonary function,Bronchial asthma,Liver & Kidney diseases (including renal& biliary colics),Endocrine diseases (myxedema & adrenal insufficiency),Elderly, infants, neonates or during child birth, With MAOI
- Meperidine – Pethidine has an effective Kappa Agonistic activity, and has an atropine like actions, used in obstetric analgesia, and is the drug of choice in severe visceral pain; renal & biliary colics
- Both **Morphine** and **meperidine** are used as pre-anesthetics.
- Tramadol is used in **Mild - Moderate acute & chronic visceral pain & during labor.**
- **Fentanyl more potent than morphine and meperidine has less** respiratory depression and CV effects.
- **Methadone is used** to treat opioid (morphine as such) withdrawal
- Naloxone and naltrexone(longer duration of action) are opiod antagonists.
- They are used to treat respiratory depression caused by opioid overdose & to reverse the effect of analgesia on the respiration of the new born baby.
- They are not used to treat opiod withdrawal