pharmacology
Team 438

MED438
KING SAUD UNIVERSITY

Reviewed by Razan AlRabah & Ibrahim AlDakhil

Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Management of Pain

Objectives

By the end of the lecture , you should know:

- Categorize the different classes of drugs used to relieve pain.
- Detail on the mechanism of action,pharmacokinetics and pharmacodynamic effects of morphine and its synthetic derivatives.
- Hints on the properties and clinical uses of morphine antagonists.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

What is pain?

- It is an unpleasant sensory & emotional experience associated with actual & potential tissue damage, or described in terms of such damage .
- The 5th vital sign suggests that assessment of pain should be as automatic as taking a client's BP and pulse.

Why should we treat pain?

- Pain is a miserable experience.
- Pain is the most common reason patient seek medical advice.
- Impairs the patient functional ability & psychological well being .
- Pain increases sympathetic output → Increases myocardial oxygen demand and Increases BP, HR .
- Pain limits mobility→ Immobility Increases risk for DVT (Deep vein thrombosis) and PE (Pulmonary embolism) .

Who 3-step analgesic ladder

1. Mild pain → non-opioid ± Adjuvant (Aspirin, Acetaminophen, NSAIDs)
2. Moderate pain → opioid ± non-opioid ± Adjuvant(Codeine, hydrocodone)
3. Severe pain → opioid ± non-opioid ± Adjuvant(Morphine,Hydromorphone)

Classes of Drugs used in management of pain

NSAIDs

-Generally the **first class** of drugs used for controlling pain.

-**Work at site of tissue injury** [1] to prevent the formation of the nociceptive mediators "pain mediators: serotonin, prostaglandine, Histamine"

-Can decrease opioid use by ~30% therefore decreasing opioid-related side effects.

-They neither cause tolerance or dependence.

-Has a ceiling effect to analgesia[2].

Adjuvant drugs [3]

-Primarily indicated for clinical conditions other than pain .

-May **modify the perception of pain** & remove the concomitants of pain such as anxiety, fear, depression .

- e.g :
  - Anxiolytics
  - Neuroleptics
  - Antidepressants
  - Antiepileptics

Opioids

-Opium is derived from the juice of the opium poppy, Papaver somniferum.

-The **natural** products include **morphine**, codeine, papaverine and thebaine

-**Opiates** are drugs derived from opium and semisynthetic and synthetic derivatives.

-Endogenous opioid peptides[4], e.g :
  - Endorphins
  - enkephalins
  - Dynorphins
  - β- endorphin

1-work peripherally , Not in the CNS
2-Maximum effect to analgesia, even when we increase the dose the efficacy is still the same
3- improves sign and symptoms , usually don't affect pain
4- when we have severe pain, naturally secreted by the body

Opioids

Classification of opioids (according to)

Source

- **Natural** → Morphine
- **Semisynthetic** → Heroin
- **Synthetic** → Pethidine, Methadone Tramadol, Fentanyl .

Agonistic & Antagonistic actions

- **Agonists** → Morphine, Codeine, Partial agonists→ Pethidine, Methadone .
- **Antagonist** → Naloxone , Naltrexone .
- **Mixed**→ pentazocine

Their specificity of action on receptors

Example:
-μ receptor agonists → Morphine, codeine, heroin.
-agonist at **k** receptor & antagonist at **μ** → Pentazocine.

Opioids exert their pharmacological actions through 4 types of receptors[1]:
All of the 4 receptors are typical G-protein coupled receptors

- **μ (mu)** (The strongest one)
  - **mu 1 :**
    -Euphoria[2] .
    -supraspinal analgesia (brain) .
    -confusion.
    -dizziness.
    -nausea.
    -low addiction potential.
  - **mu 2:**
    -Respiratory depression.
    -CVS & GIT effects.
    -miosis.
    -urinary retention.
- **K (kappa)**
  - **Kappa:**
    -spinal analgesia.
    -dysphoria.
    -psychomimetic effects .
    -feed back inhibition for endorphins system .
- **δ (delta)**
  - **Delta:**
    -spinal analgesia.
    -CVS depression.
    -decreased of brain and myocardial O2 demand.
- **OLR-1** (Opioid like receptor-1, also called orphanin.
  - **Nociceptin receptor[3]:**
    Antagonizes dopamine transport

1- these receptors mainly in brain and spinal cord and some of them in periphery
2-pleasant floating sensation without anxiety
3-an endogenous opioid peptide receptor .

Mechanism of action of opioids

1- Binding to **presynaptic** opioid receptors coupled to Gi (inhibitory G protein) .

→ ↓ AC(adenylate cyclase) & cAMP.

→↓ voltage-gated Ca2+ channels (inhibit influx of Ca2+) .

→ reduce release of neurotransmitter.

→ ↓ excitatory transmitter.

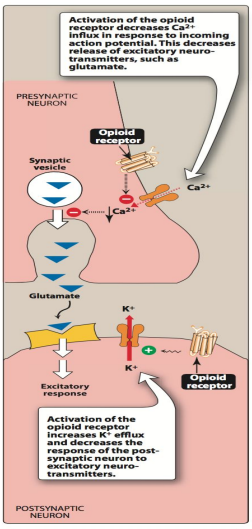


Figure 14.2
Mechanism of action of μ-opioid receptor agonists in the spinal cord.

2-Binding to **postsynaptic** receptors .

→ ↑ opening of K+ channels (hyperpolarization)

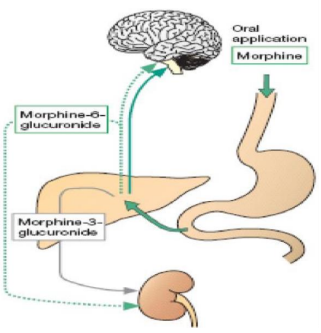
→↓ neuronal excitability.

Pharmacodynamics actions of morphine

1. **Analgesia**(Severe & visceral pain) [in acute & chronic pain]
2. **Euphoria and sedation**
3. **Respiratory depression** [1]
4. **Depression of cough reflexes** [2]
5. **Nausea & vomiting** → ↑ excitation CRTZ
6. **Pin point pupil (Miosis)**[3]
7. **Releases histamine from mast cells**[4]
8. **Effects on GIT:**
   - ↑ in tone, ↓ motility of intestine → severe constipation.
   - Constriction of biliary sphincter + contraction of gall bladder → ↑ pressure in the biliary tract.
   - depress renal function.

Pharmacokinetics of morphine

- T ½ is 2-3 h
- It is slowly and **erratically** absorbed orally (bioavailability 20-40%) → Given SC, IM, or IV injection.
- Metabolized by conjugation with glucuronic acid.
- Undergoes enterohepatic recycling
- Crosses BBB.
- Crosses Placenta.



1- By reduction of the sensitivity of respiratory center neurons to carbon dioxide.
2- Some of the opioid drugs can be added to cough syrup (codeine and not morphine because morphine is strong)
3- Used as a feature of addiction
4- Causing: warm and flushing → increases body temperature

Opioids

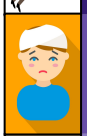
Clinical indications of morphine

- **Pain control**
  - In cancer pain, severe burns, trauma, Severe visceral pain
    "eg : abdominal , pelvic , thoracic
    " (not in renal colics/biliary colics, acute pancreatitis) [1]
- **Pulmonary edema** [2]
- **Myocardial ischemia** [2]
- **Non painful conditions**
  e.g : heart failure (to relieve distress)
- **Pre anesthetic medications**

Adverse effects of morphine

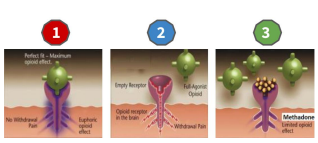
- **I**tching
- **C**onstricted **P**upil
- 
  I **P**unched **S**imon's **N**ose **R**epeatedly *Crack* *Crack*
- **R**espiratory Depression
- **CVS:** [3] hypotension(↓ systole, diastole) on long term use
- **S**edation
- **N**ausea and Vomiting
- **C**onstipation

Contraindications of morphine

 **Elderly**	more sensitive due to → ↓ Metabolism (due decrease liver function), lean body mass and Renal function. → Toxicity
 **Head injury**	Because morphine depresses respiration → accumulation of CO2 → dilatation of BV → increase intracranial pressure → patient may have hemorrhage.
 **Patients taking MAOIs** (enzyme inhibitors)	MAOIs = enzyme inhibitors. , could cause morphine toxicity
 **pancreatic pain and Biliary colic**	Because it causes constriction of the sphincters
 **Infants, neonates, or during childbirth**	→ ↓ conjugating capacity [4] → accumulation →↓respiratory level.
 **Bronchial asthma or Impaired Pulmonary Function**	Because it causes respiratory depression & bronchoconstriction due to histamine.

1- Because it constricts the sphincters and contract biliary tract
2-Because opioids causes vasodilation which decrease preload and afterload
3- In chronic use
4-during labor , we don't give mother morphine because its metabolized by conjugation with glucuronic acid which is not active in the infant →Morphine will accumulate→ toxicity and respiratory depression to the infant

Other opioid agonist drugs

Drugs	Pharmacodynamics	Indications	ADRs
Codeine	Natural , **μ** Agonist	● Used in mild & moderate pain (systemic) ● cough ● Diarrhea	Dependence < morphine
TRAMADOL [1]	●Synthetic, **μ (mu)** agonist ●less potent than Morphine. → so it is weak Analgesic. ●Inhibits NE and 5HT reuptake. —————————— **Pharmacokinetics :** Can be given orally → more oral bioavailability than morphine .	●Mild to moderate acute and chronic visceral pain. ●During labor , because it's metabolized by alkylation so it's not dangerous to the infant .	- **Seizures** [2] **(not use w\ epileptics)** -Nausea - Dry mouth - Dizziness - Sedation - Less ADRs on respiratory and CVS
PETHIDINE (meperidine)	●Synthetic, more effective **k (kappa)** agonist. ●Less analgesic, constipating, depressant on fetal respiration than morphine. ●No cough suppressant effect. ●Has atropine-like action (smooth muscle relaxant)	● As in Morphine but **not in cough and diarrhea**. ● Better preanaesthetic medication . ● Used in obstetric analgesia (no decrease in respiration) ● **Used in severe visceral pain; renal and biliary colics (smooth muscles relaxant).** [3]	- Tremors, convulsions, hyperthermia, hypotension. - Blurred vision, dry mouth, urine retention (atropine- like effects). -Tolerance and addiction
FENTANYL	Synthetic, **μ (mu)** agonist, more potent than Pethidine and Morphine -About 100 times stronger than morphine, we can use very low dose of Fentanyl and get the same action as morphine.	● Analgesic supplement during anesthesia (IV or intrathecal). ● Induce and maintain anesthesia in poor-risk pts (stabilizing heart). ● Used in combination with Droperidol (antipsychotic) as NEUROLEPTANALGESIA. ● In cancer pain and severe postoperative pain; (transdermal patch changed every 72 hrs).	- **Respiratory depression** (more serious than morphine) . We need to use in small dose and monitor respiration - CV effects are less. - Bradycardia may still occur.
METHADONE	●Weaker synthetic **μ** agonist. —————————— **Pharmacokinetics :** T1/2 = 55 hrs [4]	Used to treat and control opioid withdrawal (as patches) , [5] 	In **non-addicts**, it causes tolerance and dependence but not as severe as that of Morphine.
AT-121	●Experimental analgesic, 100 times more potent than morphine. ●A bifunctional analgesic , acting as an agonist at both the μ-opioid receptor and the nociceptin Receptor. ●The interaction with the nociceptin receptor blocks the abuse and dependence-related side effects.		

1- Tramadol is the most common.
2- with chronic use
3- best choice in patient with. visceral pain : renal and biliary colics
4- dose difficult to titrate , effect is not proportional to the dose
5- in addicted people opioid receptors are always excited and need more morphine so withdrawal symptoms appear.
When methadone bind to opioid receptor it's limit opioid effect by inhibit binding of morphine "heroin "and patient will not suffer from withdrawal symptoms because receptor occupied with methadone.

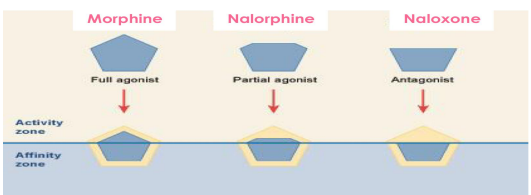
opioid Antagonist drugs

Antidotes

Competitive antagonists that bind to the opioid receptors with **higher affinity** than agonists but do **not activate the receptors**. This effectively blocks the receptor, preventing the body from responding to opioids.

	NALOXONE Pure opioid antagonist	NALTREXONE Very similar to Naloxone
P.K	Effects lasts only for 2-4 hrs.	Longer duration of action. T1/2 = 10hrs
Indications	● Used to treat and reverse respiratory depression caused by opioid overdose. ● Reverse the effect of analgesia on the respiration of the new born baby.	
ADR's	● Precipitates withdrawal syndrome in addicts. " because patient needs more morphine"	

Morphine has the highest affinity " full agonists And full activity.
Nalorphine : good affinity zone
Has three actions :
1- analgesic drug
2- partial agonist
3- Partial antagonist
Naloxone total : no activity zone , when it's bind to opioid receptor = Total antagonist **"pure opioid antagonist "**



Tolerance and Dependence in Opioids

"Morphine" " with chronic use "

Tolerance	VS	Dependence
Tolerance occurs when the person takes a **higher dose** of the drug to achieve the **same level of response** achieved initially .		Dependence develops when the neurons **adapt to the repeated drug exposure** and **only function normally in the presence of the drug**
• Occurs rapidly with opioids (e.g. morphine 12–24 hours) • Develops to respiratory depression, analgesia, euphoria and sedation. • Miosis doesn't get affected by tolerance, so addicts' pupils will still be constricted, which means that it can be an advantage in detecting addicts		• Physical dependence(abstinence) → withdrawal manifestations develop upon stoppage. • Lasts for a few days (8-10 days) in form of ↑ body ache, insomnia, diarrhea, goose flesh, lacrimation. •Psychological dependence lasting for months / years → craving. • Addiction symptoms might appear after giving an antidote

Quiz

MCQ

- **Q1:** 30 years old patient admitted to the hospital complaining from a severe visceral pain , diagnosis shows that he have biliary colics , which one of the following analgesic drugs should be prescribed to relieve his pain ?

A- morphine. **B-codeine.** **C-tramadol.** **D-pethidine.**

- **Q2:** which one of the following actions will happen when the morphine bind to the presynaptic opioid receptor.

A- inhibit influx of Ca2+. **B-influx of Ca2+ .** **C-hyperpolarization.** **D-depolarization.**

- **Q3:**which one of the following analgesic drugs has mixed agonistic and antagonistic actions ?

A- heroin. **B-fentanyl.** **C-pentazocine.** **D-naloxone.**

- **Q4:**During labor , a patient was given pethidine. the new born suffered from Respiratory depression from the analgesia. which of the following can be given to REVERSE the effect of analgesia on the respiration of the new born baby?

A-Methadone. **B-Fentanyl.** **C-Naloxone.** **D-Tramadol.**

- **Q5:**Mohammed underwent a surgery but suffered from severe postoperative pain. He was given transdermal patches of Fentanyl. which of the following is MOST LIKELY to develop?

A-respiratory depression. **B-biliary colic.** **C-dry mouth.** **D-seizures.**

SAQ

Case 1 :

Abdullah has been taking morphine intravenously for 10 days to relive the trauma pain in his ankle comes from a football match.
After he stopped using morphine , withdrawal manifestations occurs in form of body ache, insomnia,diarrhea, goose flesh, lacrimation.

Q1: define dependence .

Q2: mention one drug should be prescribed to control Abdullah's withdrawal manifestations .

Q3: name the target receptor for the drug you mentioned in **Q2** .

Answers:

MCQ

Q1	D
Q2	A
Q3	C
Q4	C
Q5	A

SAQ

Q1	Dependence develops when the neurons adapt to the repeated drug exposure and only function normally in the presence of the drug .
Q2	Methadone
Q3	μ receptor

pharmacology

Team 438

Good Luck , Future Doctors!

Team Leaders:

May Babaeer Zyad Aldosari

This Stunning Work Was Done By:

Abdullah Alassaf

Share with us your ideas !