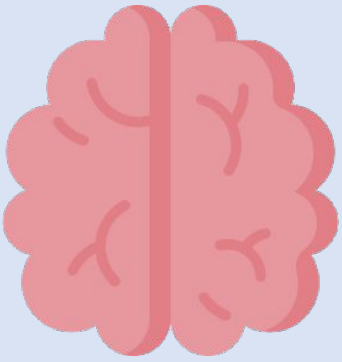


Revised & Approved

Abdullah Alsubaihi
Rania Almutiri

Pharmacology 439

MED439

Neuropsychiatry Block

Pharmacology Team 439

Color index:

Main Text

Important

Dr's Notes

Female Slides

Male Slides

Extra

Drugs Used in Management of Pain

Objectives:

1- Categorize the different classes of drugs used to relieve pain.

2- Detail on the mechanism of action pharmacokinetics & pharmacodynamic effects of morphine & it's synthetic derivatives

3- Hints on the properties & clinical uses of morphine antagonists.

Editing file

1

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" suggesting that assessment of pain should be as automatic as taking a client's BP and pulse

2

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).

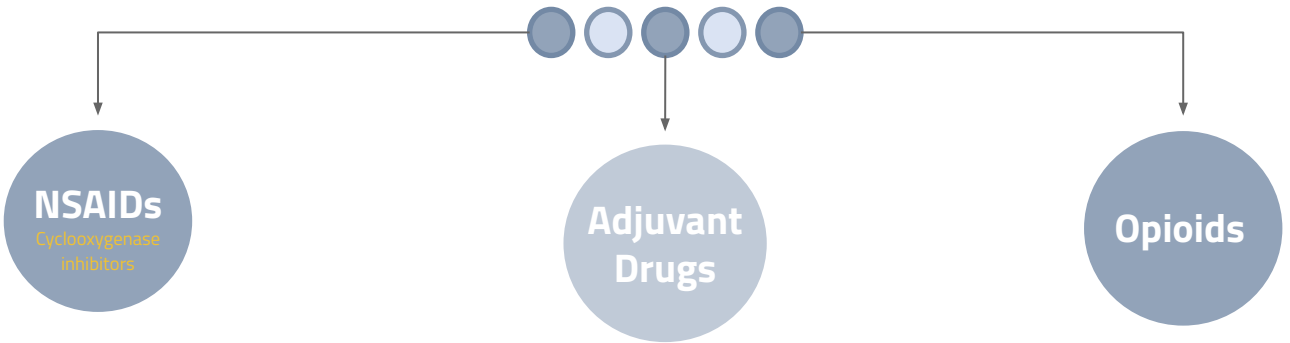
3

WHO 3-step analgesic ladder:

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

Why do we use drugs from different families? To reduce possible side effects

Classes of Drugs used in management of pain



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

- **Work at site of tissue injury** (work peripherally) to prevent the formation of the nociceptive mediators.

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

- They neither cause tolerance or dependence.

- Has a ceiling effect to analgesia (meaning it has a maximum effect so ↑ the dose doesn't ↑ the analgesic effect)

- NSAIDs are not effective in relieving severe pain

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

- Primarily indicated for clinical conditions other than pain
E.g:
- Anxiolytics
- Neuroleptics
- Antidepressants
- Antiepileptics

- In case of neuropathic pain, these drugs are more effective than opioids

- Opium is derived from the juice of the opium poppy, Papaver somniferum.
- The **natural** products include **morphine**, codeine, papaverine and thebaine.
morphine and codeine have narcotic effect, papaverine does not, and it is used as muscle relaxant
- **Opiates** are drugs derived from opium (natural) and semisynthetic and synthetic derivatives.
The term "opioids" resembles both
1- Opiates which are natural products
2- Endogenous opioids

- Endogenous opioid peptides, e.g:
- Endorphins
- Enkephalins
- Dynorphins
- β- endorphin

Classification Of Opioids

Source 

Natural
Morphine, Codeine

Synthetic:
Pethidine, methadone
tramadol, fentanyl.

Semi-synthetic:
Heroin

Action on Receptor

Opioids exert their pharmacological actions through 4 types of receptors.
All of the 4 receptors are typical G-protein coupled receptors

-Morphine, codeine,heroin are **μ** receptor agonists
-Pentazocine agonist at **K** receptors & antagonist at **μ** receptors

Agonist & Antagonist

Pure **Agonists**
Morphine, Codeine
Partial agonists:
Pethidine, Methadone

Pure **Antagonists**
Naloxone, Naltrexone

Mixed
(agonist on one type of receptor and antagonist on another)
Pentazocine

Opioid Receptors

Anatomical distribution mainly in brain, spinal cord, few in the periphery.

μ

mu 1:
- Supraspinal analgesia (brain)
- Euphoria
- Confusion, dizziness, nausea
-Low addiction potential.

mu 2:
- Respiratory depression
- CVS & GIT effects
- Miosis
- Urinary retention.

K

Kappa:
- Spinal analgesia.
- Dysphoria.
- Psychomimetic effects.
- Feedback inhibition for endorphins system.

δ

Delta:
- Spinal analgesia.
- CVS depression.
- Decreased of brain and myocardial O_2 demand.

ORL-1

Opioid-Receptor-Like subtype 1 or Orphanin

Nociceptin receptor:
Antagonizes dopamine transport
- Nociceptin (endogenous opioid) is structurally similar to dynorphin.

MOA of Opioids

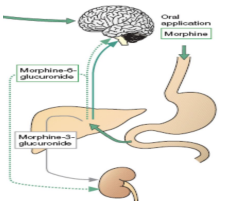
1) Binding to **presynaptic** opioid receptors coupled to Gi (inhibitory G protein) ⟶ ↓AC (adenylate cyclase) & cAMP ⟶ ↓ voltage- gated Ca^{2+} channels (inhibit influx of Ca^{2+}) ⟶ reduce release of neurotransmitter ⟶ ↓ excitatory transmitter.

2) Binding to **postsynaptic** receptors ⟶ ↑ opening of K^+ channels (hyperpolarization) ⟶ ↓ neuronal excitability.

Morphine

P.K

- T ½ is 2-3 h
- It is slowly and erratically (irregularly) absorbed orally (low bioavailability 20-40%) ⟶ Given SC, IM, or IV injection.
- Metabolized by **conjugation with glucuronic acid** by Glucuronyl transferase.
- Undergoes enterohepatic recycling
- Crosses BBB.
- Crosses Placenta. Can cause depression & addiction to the fetus



P.D

1. Analgesia [in acute & chronic pain] (sensory & emotional analgesia)
2. Euphoria and sedation
3. Respiratory depression. (ADR in high doses)
4. Depression of cough reflexes. #Respa: opiods used as central antitussive drugs
5. Nausea & Vomiting ⟶ ↑ excitation CRTZ. but after some time it becomes inhibitory to the vomiting center
6. Pin point pupil (Miosis) by stimulation of the oculomotor centre in the brain. This is **diagnostic for morphine addiction**, tolerance does not occur to it
7. Releases histamine from mast cells ⟶ flushing and edema.
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.

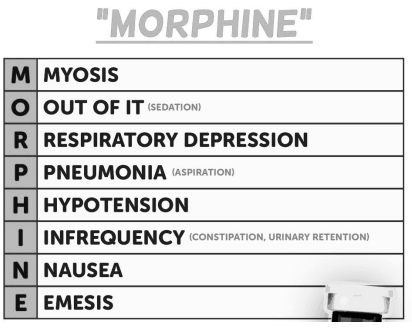
Clinical indications

- Pain control: in cancer pain, severe burns, trauma, severe visceral pain (e.g. abdominal, pelvic, thoracic) NOT in renal colics/biliary colics, acute pancreatitis, because it contracts the walls and constrict the sphincter of the bile duct.
- Pulmonary edema. morphine is a venodilator ⟶ ↓ preload & afterload ⟶ ↓edema.
- Myocardial ischemia. Stimulates vagal nucleus, veno and vasodilator, ↓ anxiety & panic
- Non-painful conditions e.g. heart failure (to relieve distress)
- Pre anesthetic medications to ↓ anxiety & pain.

Morphine

ADRs

- Itching due to histamine release.
- Constricted Pupil (Miosis)
- Respiratory Depression
- Sedation
- Nausea and vomiting due to excitation of CRTZ
- Constipation due to ↓ motility of intestine
- CVS: hypotension (↓ systole, diastole) on long term use.
- Important to monitor respiration and BP.
- ↑ ICP



Contraindication

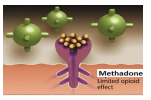
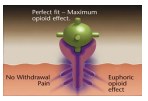
- Elderly: more sensitive due to ↓ Metabolism (due to ↓ liver function), lean body mass & renal function ⟶ Toxicity.
- Infants, Neonates, or during childbirth: Lack the enzyme Glucuronyl transferase (which is essential for metabolism) ⟶ ↓conjugating capacity ⟶ accumulation ⟶ ↓ respiratory level ⟶ may cause death.
- Head injury: morphine depresses respiration ⟶ accumulation of CO_2 ⟶ dilatation of blood vessels ⟶ ↑ ICP ⟶ hemorrhage.
- Patients taking MAOIs: Enzyme inhibitors, could cause morphine toxicity
- Pancreatic pain & biliary colic: causes constriction of the sphincters
- Bronchial asthma or impaired pulmonary function: causes respiratory depression & bronchoconstriction due to histamine.

Other opioid agonist drugs

Drug	Pharmacodynamics	Indications	ADRs
Codeine	Natural, μ agonist	- Used in mild & moderate pain (systemic) - Cough - Diarrhea ↓ motility	Dependence < morphine
Tramadol Most commonly used	- Synthetic, μ agonist - LESS potent than Morphine. (weak analgesic) - Inhibits NE and 5-HT reuptake.	**P.K:** Can be given orally (more oral bioavailability than morphine) not metabolised by conjugation, but alkylation. - Mild to moderate acute and chronic visceral pain. - During labor metabolized by alkylation so it's not dangerous to infants	- Seizures (not used with epileptics) with chronic use - Nausea - Dry mouth - Dizziness - Sedation - Less ADRs on respiratory and CVS
Pethidine (meperidine)	- Synthetic, more effective K agonist. - LESS analgesic, constipating, depressant on fetal respiration than morphine. Can be used in labor because it is metabolized by oxidation instead of Glucuronyl transferase - 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) Unlike morphine - Used in severe visceral pain; **renal and biliary colics** (smooth muscles relaxant). Unlike morphine **Best choice** in patient with visceral pain, renal & biliary colics & pancreatic pain, because of atropine-like effect.	- Tremors, convulsions - Hyperthermia - Hypotension. - Blurred vision, dry mouth, urine retention (atropine-like effects). - Tolerance and addiction
Fentanyl	Synthetic, μ 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). Could be used as transdermal patch in cancer patients - Induce and maintain anesthesia in poor-risk pts (stabilizing heart) used during heart surgery. - Used in combination with Droperidol (antipsychotic) as NEUROLEPTANALGESIA.[1] - In cancer pain and severe postoperative pain; (transdermal patch changed every 72 hrs).	- Respiratory depression (more serious than morphine) especially if given I.V (patch is safer). We need to use in small dose & monitor respiration. - CV effects are less. - Bradycardia may still occur.

1) An anesthetic process that involves combining a major neuroleptic tranquilizer/antipsychotic (typically the potent D2 receptor antagonist droperidol) and the potent opioid analgesic fentanyl to produce a detached, pain-free state, but still conscious. Even though the patient is conscious, he can't remember the operation. Refer to General anesthetic lecture for more details.

Other opioid agonist drugs, cont.

Drug	Pharmacodynamics	Indications	ADRs
Methadone	Weaker synthetic μ agonist. **P.K:** T1/2 = 55 hrs (dose difficult to titrate, effect is not proportional to the dose)	Used to treat and control opioid withdrawal (as patches)[1] - we give methadone while ↓ morphine.   with Methadone   Opioid Addiction	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) In addicted people opioid receptors are always excited and need more morphine so withdrawal symptoms appear. When methadone bind to opioid receptor it limits opioid effect by inhibit binding of morphine "heroin" and the patient will not suffer from withdrawal symptoms because the receptor is occupied with methadone. -Team438

Tolerance and Dependence in Opioids

"Morphine" "with chronic use "

Dependence VS Tolerance

- Dependence develops when the neurons **adapt to the repeated drug exposure** and **only function normally in the presence of the drug**

- 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.

- Tolerance occurs when the person takes a **higher dose** of the drug to achieve the **same level of response** achieved initially.

- Occurs rapidly with opioids (with 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.

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. Used in diagnosis & to treat overdose

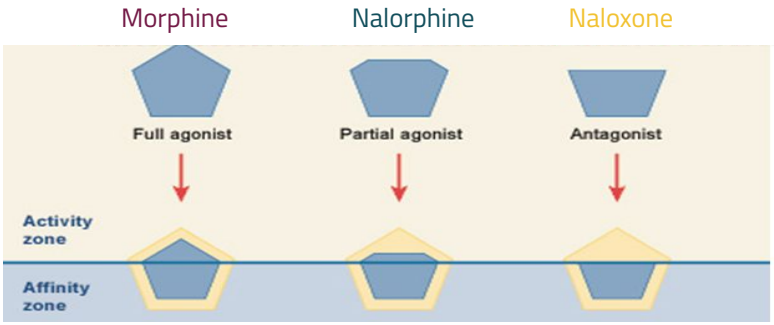
Drug	Pharmacokinetics	Indications	ADRs
Naloxone (Pure opioid antagonist)	Effects lasts only for 2-4 hrs Competitive blocker of μ1 receptor	• Used to treat & reverse respiratory depression caused by **opioid overdose** (toxicity). Give to **normal** Individuals only not addicts. • Reverse the effect of analgesia on the respiration of the new born baby.	Precipitates **withdrawal syndrome** in addicts. Displaces agonist opioids from μ receptor. **C.I in addicts, if they OD'd keep them on ventilators only.**
Naltrexone (Very similar to Naloxone)	Longer duration of action. T1/2 = 10hrs		

X = BLOCK, t = longer DOA

Morphine has the highest affinity and full activity.

Nalorphine: Good affinity zone, has three actions:
1- Analgesic.
2- Partial agonist (act on μ & K).
3- Partial antagonist.
Used to be used as an opioid antidote, now replaced by naloxone & naltrexone because they're pure antagonists.

Naloxone: No activity zone, total antagonist. -Team438



Extra information from the powerpoint notes

Three major classes of opioid receptors (μ, δ, and κ) have been identified in various nervous system sites and in other tissues, All are members of the G protein-coupled family of receptors. (mu)-opioid receptor, the major analgesic opioid receptor (delta) and (kappa) receptors.

Orphanin: Opioid-receptor-like subtype 1 (ORL1). the fourth and most recently discovered member of the opioid receptor superfamily. Its endogenous ligand has been termed **nociceptin**. Nociceptin is structurally similar to dynorphin except for the absence of an N-terminal tyrosine; it acts only at the ORL1 receptor. Nociceptin is a peptide related to the opioid class of compounds (ex. morphine and codeine), but it does not act at the classic opioid receptors (namely, mu, kappa, and delta opioid receptors) which typically act as pain relievers. Nociceptin is widely distributed in the CNS and dorsal horns of the spinal cord. This receptor-ligand system modulates a variety of biological functions and neurobehavior, including stress responses and anxiety behavior, learning and memory, locomotor activity, and inflammatory and immune responses.

G protein–coupled receptors (GPCRs) which are also known as seven-transmembrane domain receptors, 7TM receptors (because they pass through the cell membrane seven times), **heptahelical receptors, and G protein–linked receptors (GPLR)**, constitute a large protein family of receptors, that detect molecules outside the cell and activate internal signal transduction pathways and, ultimately, cellular responses.
The majority of currently available opioid analgesics act primarily at the μ-opioid receptor. Analgesia and the euphoriant, respiratory depressant, and physical dependence properties of morphine result principally from actions at μ receptors. In fact, the μ receptor was originally defined using the relative potencies for clinical analgesia of a series of opioid alkaloids.

Extra information from the powerpoint notes

M.O.A

Opioid agonists produce analgesia by binding to specific G protein-coupled receptors that are located in brain and spinal cord regions involved in the transmission and modulation of pain. Some effects may be mediated by opioid receptors on peripheral sensory nerve endings.
The primary afferent neuron (like here in the hand) originates in the periphery and carries pain signals to the dorsal horn of the spinal cord.
The opioids have two well-established direct Gi/0 protein-coupled actions on neurons: (1) they close voltage-gated Ca2+ channels on presynaptic nerve terminals and thereby reduce transmitter release, and (2) they open K+ channels and hyperpolarize and thus inhibit postsynaptic neurons.

Morphine

Pain consists of both sensory and affective (emotional) components, In contrast, nonsteroidal anti-inflammatory analgesic drugs, eg, ibuprofen, have no significant effect on the emotional aspects of pain.
Euphoria: intravenous morphine experience a pleasant floating sensation with lessened anxiety and distress.
Miosis is due to stimulation of oculomotor center in the CNS, No tolerance to pin point & constipation.
Histamine: flushing and warming of the skin.
Opioids have also other functions on neurotransmitters and other organs but these are the most important.

With frequently repeated therapeutic doses of morphine or its surrogates, there is a gradual loss in effectiveness; this loss of effectiveness is termed **tolerance**. 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. Gooseflesh is contraction of the muscle underneath the skin (bumpy skin) like what happen in cold or fear. **Lacrimation**: the secretion of tears
However, despite the loss of physical dependence on the opioid, craving (strong feeling to consume ..) for it may persist.

Well absorbed by injection. However, because of the first pass effect, the oral dose of the opioid (eg, morphine) to elicit a therapeutic effect may need to be much higher than the parenteral dose.
We have to give morphine frequently (every 4 h) to mainintain therapeutic efficacy.
First pass metabolism is what occurs when a drug is absorbed from the GI tract. When a drug is taken orally it is absorbed into the portal circulation (the blood vessels of the liver). Many of these drugs are very efficiently metabolized (altered for elimination) as they pass through the portal circulation during this first time. It reduces the amount of active drug that gets into the general circulation.
Enterohepatic cycling is where: Unmetabolized drugs as well as drug metabolites go through the liver and biliary tract for excretion and proceed to make their way out of the body through the intestinal tract. In other words, this is the body's way of putting them in the trash and getting rid of them.
Here's the catch. . .on the way out through the intestines (the entero part of the word enterohepatic) some of the discarded active drug gets reabsorbed back into the blood stream where it is again available to the body for use. In other words, it's being recycled. RESULT: The half life and duration of action of a drug is increased.
The glucoronides metabolites are usually inactive, but this is exception (6) part of it can be active and go again to the brain. The opioids are converted in large part to **polar metabolites (mostly glucuronides)**, which are then readily excreted by the kidneys

Visceral pain is pain that results from the activation of nociceptors of the thoracic, pelvic, or abdominal viscera (organs).
Sphincter of oddy is sharing between biliary and pancreas. PE: Morphine dilates the vein & reduce edema. MI: morphine reduce stress & pain & decrease preload. The relief produced by intravenous morphine in patients with dyspnea from pulmonary edema associated with left ventricular heart failure is remarkable. Proposed mechanisms include reduced anxiety (perception of shortness of breath) and reduced cardiac preload (reduced venous tone) and afterload (decreased peripheral resistance). However, if respiratory depression is a problem, furosemide may be preferred for the treatment of pulmonary edema. On the other hand, morphine can be particularly useful when treating painful myocardial ischemia with pulmonary edema. Distress: extreme anxiety, sorrow, or pain.

MCQs

Q1- which one of the following actions will happen when the morphine bind to the presynaptic opioid receptor			
A- inhibit Ca influx	B- Depolarization	C- Hyperpolarization	D- Ca influx
Q2: which of the following can be used to treat Opioid withdrawal symptoms?			
A- Naltrexone	B- Naloxone	C- Methadone	D- Fentanyl
Q3- which opioid is contraindicated in patients with epilepsy			
A- Morphine	B- Codeine	C- Fentanyl	D- Tramadol
Q4- A 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
Q5: Which of the following statements about fentanyl is correct?			
A- Its withdrawal symptoms can be relieved by naloxone.	B-Fentanyl is 100 times more potent than morphine	C- The active metabolites of fentanyl can cause seizures.	D- It is most effective by oral administration.
Q6: A 31-year-old female is brought to the emergency department by friends who said she has been "taking drugs." They did not know specifically what she had taken. She presents with respiratory depression and dysphoria. Stimulation of which receptor is likely causing her dysphoria?			
A- K- Opioid receptor	B- μ- Opioid receptor	C- GABA receptor	D- Serotonin receptor
Q7: A 47-year-old woman is recovering from a hysterectomy. Her physician prescribes an opioid analgesic as needed for postoperative pain. Opioids can cause many effects in addition to analgesia including constipation, respiratory depression, euphoria, miosis, and drowsiness. With prolonged use, tolerance develops to most of these effects. Which of the following effects persists in spite of tolerance leading to a decrease in the other effects?			
A- Analgesia	B- Euphoria	C- Miosis	D- Drowsiness
Q8: A 24-year-old G1P0 woman arrives at the hospital in labor at 39 weeks gestation. She denies an epidural, stating her desire to give birth naturally. After 5 h of labor, the baby has begun its descent through the birth canal when the patient requests pain relief. Which is a serious potential side effect for the fetus if an opioid is given to the mother for analgesia?			
A- Diarrhea	B- Hallucinations	C- Hyperthermia	D- Respiratory depression

1	2	3	4	5	6	7	8
A	C	D	D	B	A	C	D

SAQ

Q1) A 51-year-old woman was seen in the emergency department because of strong abdominal pain for the past hour. Physical examination showed a red-headed, pale-skinned woman in obvious distress, with severe pain and tenderness of the right lank.
A presumptive diagnosis of renal colic was made, and the patient was given an IM injection of an opioid drug that is a partial agonist at μ receptors and a full agonist at K receptors. Which drug was most likely administered?

Q2) A 64-year-old man suffering from advanced heart failure was admitted to the emergency department because of extreme dyspnea over the past hour. After physical examination, a diagnosis of impending pulmonary edema was made, and an appropriate therapy was prescribed that included the IM injection of morphine. What is the cardiovascular action most likely contributed to the therapeutic effect of the drug in the patient's disorder?

Q3) A patient develops overdose of an opioid. What medication can you use to treat them and what is the mechanism of action?

Q4) Mention one special feature for each of the 4 opioid receptors.

Q5) Fentanyl is combined with Droperidol to cause which type of analgesia?

Answers

A1) Pethidine

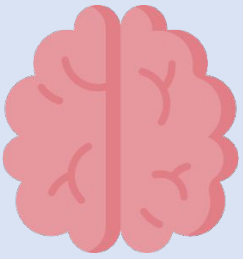
A2) Peripheral venous dilation

A3) Naloxone/Naltrexone. Competitive antagonists that bind to the opioid receptors with higher affinity than agonists but don't activate the receptors. This effectively blocks the receptor, preventing the body from responding to opioids.

A4) μ: euphoria, K: dysphoria, δ: Decreased of brain and myocardial O_2 demand, OLR-1: antagonizes dopamine transport.

A5) Neuroleptanalgesia

Feedback Form



Neuropsychiatry Block

Pharmacology Team 439

Leaders

Banan AlQady

Ghada AlOthman

Khaled Alsubaie

Organizers

- Duaa Alhumoudi
- Ghada Aljedaie
- Haya Alanazi
- Mais Alajami
- Norah Alasheikh
- Nouf Alsubaie
- Sadem Alzayed
- Shayma Alghanoum
- Tarfa Alsharidi

Note Takers

- Ghadah Alsuwailem
- Homoud Algadheb
- Omar Alhalabi
- Mishal Althunayan
- Yasmine Alqarni

Revisers

- Omar Alhalabi
- Mayasem Alhazmi
- Mishal Althunayan

Members

- Abdulaziz Alderaywsh
- Abdulaziz Alghuligah
- Abdulrahman Almebki
- Abdulrhman Alsuhaibany
- Abdurahman Addweesh
- Albandari Alanazi
- Aljoharah Albnyan
- Aljoud Algazlan
- Dana Naibulharam
- Fatimah Binmeather
- Feras Alqaidi
- Lama Alahmadi
- Maha Alanazi
- Manal Altwaim
- Mayasem Alhazmi
- Mona Alomiriny
- Norah Almasaad
- Noura Bamarei
- Rawan Bakader
- Rayan Jabaan
- Reem Alqahtani
- Salem Alshihri
- Sara Alharbi
- Sarah Alqahtani
- Shahad Almezel
- Shatha Aldhohair
- Teif Almutiri
- Yara Alasmari

@TeamPharma439@gmail.com