PHARMACOLOGY

LECTURE NO.

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Opioids

Tolerance and physical dependence:

- With repeated administration of morphine (and others), there is a gradual loss in effectiveness. This is called tolerance. : reduction the action of the drug in general
- To reproduce the original response, a larger dose is needed. Due to tolerance the dose may increase 35 times to remain effective
- Along with tolerance, physical dependence develops.

Tolerance = More down regulation receptor

Opioids

- Physical dependence is defined as a characteristic withdrawal or abstinence syndrome when a drug is stopped or an antagonist is administered.
- The mechanism is poorly understood, but may be due to any of the following:

1. Down regulation of μ receptors.
2. δ opioid receptors function as an independent component in the maintenance of tolerance.

Mu receptors are the most important kind of receptors because they're widely available in the body (peripheral receptors, many of them can be found in gi tract)

Opioids

3. **Receptor uncoupling: a dysfunction of structural interactions between the μ receptor and G proteins, second messenger systems and their target ion channel.**
4. **NMDA type glutamate receptor has been shown to play a role in tolerance development and maintenance, because its antagonist ketamine can block the development of tolerance.**

Giving ketamine to patients can improve the tolerance

Almost all drugs have tolerance effect to different degrees
Agonists usually make down regulation receptors but to different extents
Antagonists make up-regulation receptors
* simply it's adaptation to the stimuli (receptors not available to the agonist) it also can happen at the level of the gene (transcription and translation of the gene may decrease and even the modification of the protein may decrease too)

Opioids

Organ System Effects of Opioids:

A. CNS effects:

1. **Analgesia: They are effective in the two aspects of pain experience, the sensory and affective (emotional) components.**
2. **Euphoria: After IV administration of morphine, patients or users experience a pleasant floating sensation with lessened anxiety or distress.**

*Your perception (in the cortex)of pain will be different when you take an opioid , not just suppressing it

Opioids

- Sometimes dysphoria occurs, which is an unpleasant state characterized by restlessness and malaise (توعك). Different types of receptors so different actions and outcomes

3. Sedation: Drowsiness and clouding of mentation, with little or no amnesia. لـ فقدان الذاكرة

No hypnosis
Elderly patients >65 may fall asleep

- Sedation is less frequent with meperidine and fentanyl.

Using during anesthesia for surgeries, highly potent analgesic, and short half life, repeated administering, but it's used as analgesic not anesthesic

When do we use amnesia?
1.Labor; we dont give them opioids because it causes less contractions ,at the end of labor we give the patient a specific benzodiazepine : midazolam so she will fall asleep and complete the delivery without remembering anything.
2.endoscopy

Opioids

- **Sleep is induced more in the elderly than the young, but the patient is easily aroused from this sleep.**

4. **Respiratory depression: They inhibit brainstem respiratory center → Increase in alveolar PCO_2 and depressed response to a carbon dioxide challenge.**

Inhibition of respiration = hypopnea(accumulation of co2) or apnea(stop respiration)

No hyperventilation within opioids
Hypercapnia /brain cerebral vasodilation /increase pressure specially in the optic nerve—> blindness or reduction of vision

Opioids

5. **Cough suppression: Codeine and Dextromethorphan is used for this purpose. Cough suppression may lead to accumulation of secretions in the airway with obstruction and atelectasis.** ⇒ leads to infection

This drug has no systemic effects, just suppressing the cough

6. **Miosis: Constriction of the pupil even in highly tolerant addicts.** No tolerance

- **Miosis is a sign of opioid overdose or abuse.**

or parasympathetic stimulation

Opioids

- **Miosis is mediated by parasympathetic pathways, and is blocked by both opioid antagonists and atropine.** antimuscarinic

7. **Truncal rigidity: Results from an action at supraspinal level.** Interfere with ventilation (not relaxed enough to take a deep breath) accumulation of co2

- **It reduces thoracic compliance and interferes with ventilation.**
- **It can be overcome by opioid antagonists.**

Opioids

Crt-z: base of the brain where there's no bbb = anything in circulation which can stimulate it will affect it because there's no bbb or it's developed enough (these chemicals will enter cns)

8. **Nausea and vomiting: by stimulation of the brainstem chemoreceptor- trigger zone (CRT-Z). It has a vestibular component.** ⇒ Which will stimulate vomiting centre

9. **Temperature:**

We're talking here about overdose not regular doses

- **Hyperthermia is produced by μ receptor agonists.**
- **Hypothermia is produced by κ receptor agonists.**

Opioids

B. Peripheral effects:

I. Cardiovascular system:

1. Most opioids produce **bradycardia**.
2. **Meperidine (pethidine)** has antimuscarinic action and can produce **tachycardia**.
3. **Hypotension** due to **vasodilation** (attributed to depression of the vasomotor center and release of histamine).

It can block muscarinic receptors ,also can make miosis by stimulating parasympathetic pathways but not as effective as other drugs

Vasodilation = hypotension, preload and afterload reduction

hypotension → Can't walk steady

Opioids

- **Hypotension is especially important in the stressed heart and in the presence of hypovolemia.**
- **Bradycardia and hypovolemia can lead to postural hypotension.**

and vasodilation

4. **Cerebral vasodilation is associated with respiratory depression and accumulation of CO_2 leading to increased cerebral blood flow and elevation in intracranial pressure.**

Which affects the optic nerve

Opioids

II. GIT:

- **Opioid receptor exist in high density in the GIT.**
- **Constipation as a result of an effect on the enteric nervous system and CNS.** Mu receptors
- **Stomach motility decreases but tone increases and gastric acid secretion decreases.**

Tone increases in all gi tract, biliary system, renal system &uterus.
Contractions decreases so delay in gastric emptying ,so if the patient takes another medication it will stay in their stomach for a longer time and this will affect the absorption of the drug (drug-drug interaction)

Opioids

- **Small intestine tone is increased but the amplitude of nonpropulsive contrations is markedly decreased.**
- **Large intestine propulsive contractions decrease but tone is increased → delays the passage of fecal mass and allows increased absorption of water → constipation (is the basis for their use in treatment of diarrhea).**

Treatment of diarrhea is treatment of cause, but if we diagnosed the patient and couldn't figure out the cause we give them opioids.(certain opioids which have lesser systemic effects)

Opioids

III. Biliary tract:

1. **Contract biliary smooth muscle → biliary colic.** Opioids will make the situation worse
2. **Contraction of the sphincter of Oddi → reflux of biliary and pancreatic secretions and elevated plasma amylase and lipase levels.**

IV. Uterus:

⇑ tone ↑ contraction & blockade of blood vessels ↑ pain in smooth muscles

- **May prolong labor.** Tone increases not contractility in uterus

Opioids

V. Renal system:

1. **Depression of renal function due to reduction in renal blood flow.** why?
2. **Antidiuretic effect.** Due antidiuretic hormones section → water without salt
3. **Enhance renal tubular sodium reabsorption.**
4. **Ureteral, bladder and sphincter tone are increased → urinary retention.**

- **Renal colic caused by a renal stone is made worse.**

We know that in patients with atherosclerosis, vasodilators usually work on normal vessels so diversion of blood occurs in normal vessels and ischemic area will become worse so If there's atherosclerosis, blood flow decreases in the renal system

Opioids

VI. Neuroendocrine:

- **Stimulate the release of ADH, prolactin, somatotropin but inhibit the release of LH.**

VII. Pruritus:

vasodilation

- **Flushing and warming of the skin, sweating and itching at therapeutic doses probably due both to central effect and release of histamine.**

Chemical histamine release

not allergic

Opioids

Therapeutic Uses:

1. **Analgesia: Severe, constant pain is usually relieved by opioids; whereas sharp, intermittent pain is NOT effectively controlled.**

- **Effective for pain of cancer.**
- **May make the pain of renal and biliary colic worse (increase smooth muscle tone).**

colics

Opioids

Vasodilation in veins/reduce venous return to the right side of the heart/less congestion/the heart function more efficiently/ the fluid will be lost

2. **Acute pulmonary edema:**

- **Reduce anxiety by reducing perception of the shortness of breath.**
- **Reduction of preload and afterload.**
- **Particularly useful for pain of MI associated with pulmonary edema.**

Morphine = relief the pain, reduce anxiety, improvethe venous congestion

3. **Cough suppression at doses lower than those needed to produce analgesia.**

Opioids

4. **Diarrhea:**

- **Can control all kinds of diarrhea.**
- **Diarrhea due to infection should be treated with the appropriate antibiotic.**

5. **Shivering: meperidine has the most pronounced reduction of shivering through an action on subtypes of α_2 adrenoceptors.**

6. **Anesthesia: as premedications and intraoperatively to reduce pain.**

Opioids

Routes of administration:

1. **IV**
2. **PO** → Per os → oral
3. **PR** → Per rectum
4. **Transdermal**
5. **Intranasal**
6. **buccal** → Local

Opioids

Adverse Effects:

1. **Behavioral restlessness, tremulousness** Related to fear (ارتجاف), **and hyperactivity.**
2. **Respiratory depression.**
3. **Nausea and vomiting.** Can be therapeutic effect, Apomorphine cause immediate vomiting, can be used in Gastric lavage
4. **Increased intracranial pressure**
5. **Postural hypotension.**
6. **Constipation.**

Opioids

7. **Urinary retention.** Contraction in the neck of the bladder
8. **Itching and urticaria.**
9. **Tolerance and dependence:**

A. Tolerance:

- **Begins with the first dose but becomes clinically manifest after 2-3 weeks of frequent exposure to ordinary doses.**

Opioids

- **Develops most readily with large doses given at short intervals, and is minimized by giving small doses with long intervals.**
- **The degree of tolerance can be as great as 35-fold.**
- **Can affect analgesic, sedative and respiratory depressant effect; in addition to antidiuretic, emetic and hypotensive effect but NOT miotic, convulsant and constipating actions.**

Opioids

- **The rates at which tolerance appears and disappears, as well as the degree of tolerance, may differ among different opioids and among individuals using the same drug.**
- **It may develop to agents with mixed agonist/antagonist effect but to a lesser extent than to agonists.**
- **It does NOT develop to the antagonist action of mixed agents or to those of pure antagonists.**

Opioids

- **Cross-tolerance is characteristic of opioids (for those with pure μ receptor agonist activity primarily).**
- **It affects analgesic, euphorient, sedative and respiratory depressant actions; which can be partial or incomplete.**
- **This led to the concept of "opioid rotation" for treatment of cancer pain.**

Opioids

- **Ketamine (NMDA-receptor antagonist) improves opioid tolerance.**
- **The use of drugs with δ receptor antagonist action and μ receptor agonist action may produce less tolerance. (??!! experimental).**

Opioids

B. Physical dependence:

- **The signs and symptoms of withdrawal include: rhinorrhea, lacrimation, yawning, chills, piloerection (goose flesh, قشعريرة), hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety and hostility.**
- **Administration of an opioid suppresses these signs and symptoms almost immediately.**

Opioids

- **The time of onset, intensity and duration of abstinence syndrome depend on the drug used and its half-life.**
- **With morphine and heroin, withdrawal signs usually start 6-10 hours after the last dose, peaks in 36-48 hours, and most of the effects gradually disappear by the 5^{th} day.**
- **With meperidine, withdrawal subsides in 24 hours.**

Opioids

- With methadone several days are needed to reach the peak, but it may last up to 2 weeks, and is associated with less intense immediate syndrome, and this is the basis for its use to treat heroin addicts.
- After abstinence syndrome subsides, tolerance also disappears, but craving (رغبة ملحة) for opioids may persist for many months.

Opioids

- A transient explosive syndrome – antagonist precipitated withdrawal -occurs within 3 min, peaks in 10-20 min and subsides after 1 hour.
- In case of mixed agents, withdrawal syndrome occurs after repeated administration and sudden withdrawal but is different: anxiety, loss of appetite and weight, tachycardia, chills, increase in body temperature and abdominal cramps.

Opioids

C. Psychologic dependence:

- After IV administration, euphoria, indifference to stimuli and sedation tend to promote their compulsive use.
- Addicts experience an abdominal effect similar to intense sexual orgasm.
- These factors constitute the primary reasons for opioid abuse liability and are strongly reinforced by development of physical dependence.

Opioids

Contraindications And Cautions:

1. Use of pure agonist + weak partial agonist may diminish analgesia.
2. May increase intracranial pressure in patients with head injury → Death.
3. Use in pregnancy → to physical dependence in fetus followed by withdrawal syndrome after delivery.

Opioids

4. **Patients with impaired pulmonary function → acute respiratory failure.**
5. **Impaired renal and/or hepatic function → prolong half-life of elimination.**
6. **Addisons's disease and hypothyroidism → prolonged and exaggerated response.**

Opioids

Table 31–5. Opioid drug interactions.

Drug Group	Interaction with Opioids
Sedative-hypnotics	Increased central nervous system depression, particularly respiratory depression.
Antipsychotic tranquilizers	Increased sedation. Variable effects on respiratory depression. Accentuation of cardiovascular effects (anti-muscarinic and α-blocking actions).
MAO inhibitors	Relative contraindication to all opioid analgesics because of the high incidence of hyperpyrexic coma; hypertension has also been reported.

MAO, monoamine oxidase.

Others

Tramadol:

- **Centrally acting analgesic.**
- **Mechanism of action is predominantly blockade of serotonin reuptake.**
- **Also inhibits norepinephrine reuptake**
- **It is a weak μ receptor agonist – partially antagonized by naloxone.**
- **Adverse effects include seizures, nausea, dizziness, serotonin syndrome**

Tramadol

- **No significant effects on respiration or cardiovascular system.**
- **Can be used as adjunct with pure agonists in treatment of chronic neuropathic pain.**
- **It has a weak dependence potential if used over weeks to months. There is a higher risk in drug abusers and Medical staff.**

Opioid Antagonists

Naloxone, Naltrexone, Nalmefene:

- **Have high affinity for μ receptors and lower affinity for δ and κ receptors.**

Pharmacokinetics:

- **Naloxone usually given by injection and have a short duration of action (1-2 hours). The major metabolite is the glucuronide conjugate.**

Opioid Antagonists

- **Naltrexone is well absorbed after oral administration but may undergo first pass metabolism.**

  Its half life is ~ 10 hours and duration of action up to 48 hours.
- **Nalmefene is available only for IV administration. Its half life is ~ 8-10 hours.**

Opioid Antagonists

Pharmacodynamics:

- **The are inert in the absence of an agonist.**
- **Naloxone when given to a morphine addict, it completely and dramatically reverses the opioid effects within 1-3 minutes.**
- **It normalizes respiration, level of consciousness, pupil size, bowel activity and awareness of pain.**

Opioid Antagonists

- **In dependent subjects who appear normal while taking opioids, they precipitate an abstinence syndrome.**
- **Major application of naloxone is in opioid overdose.**
- **Longer-acting antagonists are used in addicts treatment programs.**
- **No tolerance to their action occurs.**