This is the second part of the 3rd lecture
https://www.youtube.com/watch?v=SAUaaXJ3SkE

PHARMACOLOGY

LECTURE NO. **3.2**

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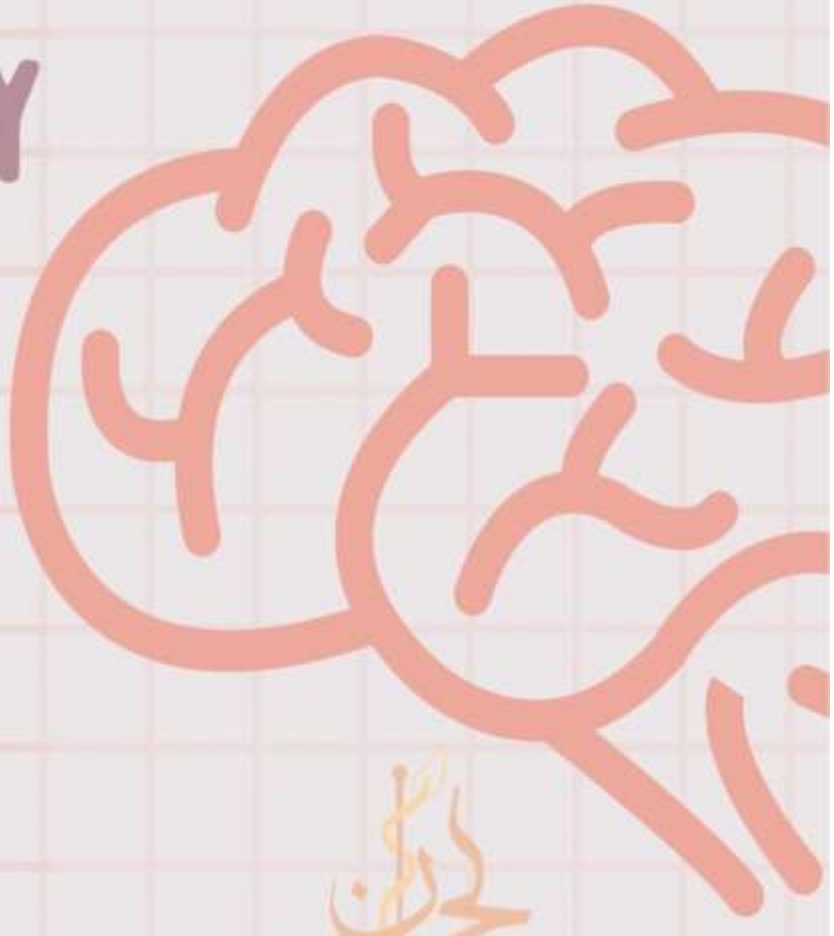

Opioids

7. **Urinary retention.**
8. **Itching and urticaria.**
9. **Tolerance and dependence:**

A. Tolerance: decreasing in the pharmacological action of the drug with continues administration

- **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 because of the continues exposure of the receptor with the drug, and is minimized by giving small doses with long intervals نزل تركيز الدوا فبطل فيه اتصال مباشر بين الدوا و الريسبتور
- and its part of the program for treating opioid abuse.
- (its an important point and it applies to many drug of abuse not only for opioids)
- The degree of tolerance can be as great as 35-fold.**it might be more or less than 35
- Can affect analgesic, sedative and respiratory depressant effect; in addition to antidiuretic, emetic and hypotensive effect but NOT miotic, convulsant and constipating actions(there is no tolerance with these things).

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. This type called partial agonist and partial antagonist**
- **It does NOT develop to the antagonist action of mixed agents or to those of pure antagonists like naloxone .**

Opioids

- **Cross-tolerance is characteristic of opioids (for those with pure μ receptor agonist activity primarily.(if the patient is tolerant to one opioid , when you give another opioid the patient may have tolerance to it immediately)**
- *** one of methods of the opioid tolerance management is to change the opioid)C (cross-tolerance ممكن يتحسن الوضع و ممكن يكون فيه)**
- **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, yawningتثاؤب, chills, piloerection (goose flesh, قشعريرة)**
- **hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety and hostility . drug العدوانية الي ممكن يقتل عشان يحصل على ال**
- **Administration of an opioid suppresses these signs and symptoms almost immediately.(and because of that we use drugs with long half live and small doses so the drug approximately ends in the body result in weaning from drug abuse)**

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 5th day.**
- **With meperidine, withdrawal subsides in 24 hours. the meperidine has some differences from other opioid ,pay attention about them**

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. severe and acute development.
- 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.(the symptoms are less than the withdrawal syndrome of agonist)

Opioids

C. Psychologic dependence:

- After IV administration, euphoria, indifference to stimuli لامبالاة and sedation tend to promote their compulsive use.فيه مرضى بوخدوه لفترات طويلة و ما بتأثروا فيه
- 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=partial antagonist may diminish analgesia.**
2. **May increase intracranial pressure in patients with head injury → Death.**
3. **Use in pregnancy →** the drug crosses the placenta and it acts in the fetus leading **to physical dependence 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 (prolong for the effect of the drug**
6. **Addisons's disease and hypothyroidism → prolonged and exaggerated response.**

Study this table

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 in the CNS.
- Also inhibits norepinephrine reuptake
- It is a weak μ receptor agonist – partially antagonized by naloxone.
- Adverse effects include seizures, nausea, dizziness, serotonin syndrome which has hyperpyrexia.

Tramadol

- **No significant effects on respiration or cardiovascular system because it's a weak opioid like agent.**
- **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

we use them clinically to treat the toxicity of opioids

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) and this may demand multiple administration of Naloxone to treat opioid adverse reaction (repeatedly) . 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.باليوم ممكن تعطيلك جرعة منه
- **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.**
- it precipitates withdrawal syndrome

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.

Opioid Mixed Agonist-Antagonist

Buprenorphine:

- **Long-acting derivative.**
- **It is a partial μ-receptor agonist (low intrinsic activity) and an antagonist at the δ and κ receptors.**
- **It can antagonize the action of more potent μ agonists such as morphine.**
- **Slowly dissociates from μ receptors. Thus, it is resistant to naloxone reversal. because naloxone is a competitive antagonist at the μ receptors so it will displace the opioid**

Opioid Mixed Agonist-Antagonist

- **It is as effective as methadone for the management of opioid withdrawal and detoxification.**
- **In contrast to methadone, high-dose administration of buprenorphine results in a μ-opioid antagonist action, limiting its analgesia and respiratory depression.**
- **Can depress respiration if combined by CNS depressants, or if given IV because in IV the initial concentration of drug is high .(ordinary dose not high dose)its relatively high**

Opioid Mixed Agonist-Antagonist

- **Psychotomimetic effects, with hallucinations, nightmares, and anxiety, have been reported.**
- **Undergoes first-pass metabolism.**
- **May be administered sublingual to bypass the liver so it won't have immediate metabolism in the liver before reaching the circulation**

Opioid Mixed Agonist-Antagonist

Nalbuphine:

- **Nalbuphine is a strong κ-receptor agonist and a partial μ-receptor antagonist.**
- **It is given parenterally.**
- **Respiratory depression may be resistant to naloxone reversal due to its greater affinity for the receptor than naloxone. (partial agonist=partial antagonist)**
- **Best wishes!**
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