Pharmacology

CNS

Sheet No 2

Writer: Mais Fareed

Corrector:

Doctor: Malik Zuhluf

Opioids

- Weak opioids
  - Codeine
  - Tramadol
- Strong opioids
  - Oxycodone
  - Morphine
  - Methadone
  - Fentanyl
  - Mepiridine

- We've been talking about opioids in the last lecture and in this lec we are going to talk about the characteristics of these drugs (strong and weak opioids) .
- We will start with morphine (prototype) with some words about it : used for severe pain, there is no ceiling effect for it (increasing the dose increases the activity), however we have to take of tolerance, physical dependence and psychological dependence.
- You have to be aware of the variation between patients, if the patient was elderly (depressed CNS) the dose of morphine should be less than the dose for adults.
- Morphine is the drug of choice in many cases of severe pain
- Its adverse effects are the same of other opioids that we mentioned in the

last lecture (euphoria,nauseua, vomiting, CNS depression, respiratory depression..)

- **This slide from Katzung talking about strong opioids and morphine which is one of them you can see it's side effects and MOA as strong receptor agonist ,remember as we said in the last lec that it causes sedation not hypnosis, causes constipation because of slow GI transit, has first-pass effect duration (effectiveness) 1-4 h, but the first-pass metabolism is also high so given 4 times per day .**
- **And its toxicity (remember toxicity is deferent than adverse effects) :depression, severe constipation, addiction and convulsions (because it causes CNS depression so imbalance**

between activation and suppression so too much suppression causes convulsions) generally most of the CNS depressants cause convulsions.

Subclass	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities
Strong opioid agonists				
Morphine Methadone Fentanyl	Strong -receptor agonists	Analgesia relief of anxiety sedation slowed gastrointestinal transit	Severe pain adjunct in anesthesia (fentanyl, morphine) pulmonary edema (morphine only) maintenance in rehabilitation programs (methadone only)	First-pass effect duration 1–4 h except methadone, 4–6 h *Toxicity:* Respiratory depression severe constipation addiction liability convulsions
Hydromorphone, oxymorphone: Like morphine in efficacy, but higher potency				
Meperidine: Strong agonist with anticholinergic effects				
Sufentanil, alfentanil, remifentanil: Like fentanyl but shorter durations of action				

Morphine

- **Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, morphine may be used to supplement the sleep-inducing properties of hypnotic agents**

- **Morphine relieves diarrhea by decreasing the motility and increasing the tone of the intestinal smooth muscles**

- **Morphine produce a powerful sense of euphoria and well-being.**

- **Morphine is given orally , by injection or pump (the patient inject himself or we give him automatic pump)**
- **Morphine is also used in the treatment of acute pulmonary edema, intravenous morphine is dramatically relieve dyspnea cause by pulmonary edema associated with left ventricular failure.**
- **Metabolized in the liver and eliminated by kidney so patients with liver failure or kidney failure will be building up of morphine so we need another drug to help this patients**

Kidney

Morphine has 2 biologically active metabolites, morphine-6-glucuronide and morphine-3-glucuronide.

Morphine-6-glucuronide binds to the opioid receptor and is believed to contribute to the effects of the parent compound. Morphine-3-glucuronide does not bind to the receptor and is believed to contribute in some cases to adverse effects such as myoclonus and confusion.

Usually, the metabolites are considered a clinical issue only when their concentrations in the blood are likely to fluctuate

differently than the concentration of the parent compound. This can occur during renal insufficiency, so

Hydromorphone

- may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulation. Excreted in bile instead of kidney.

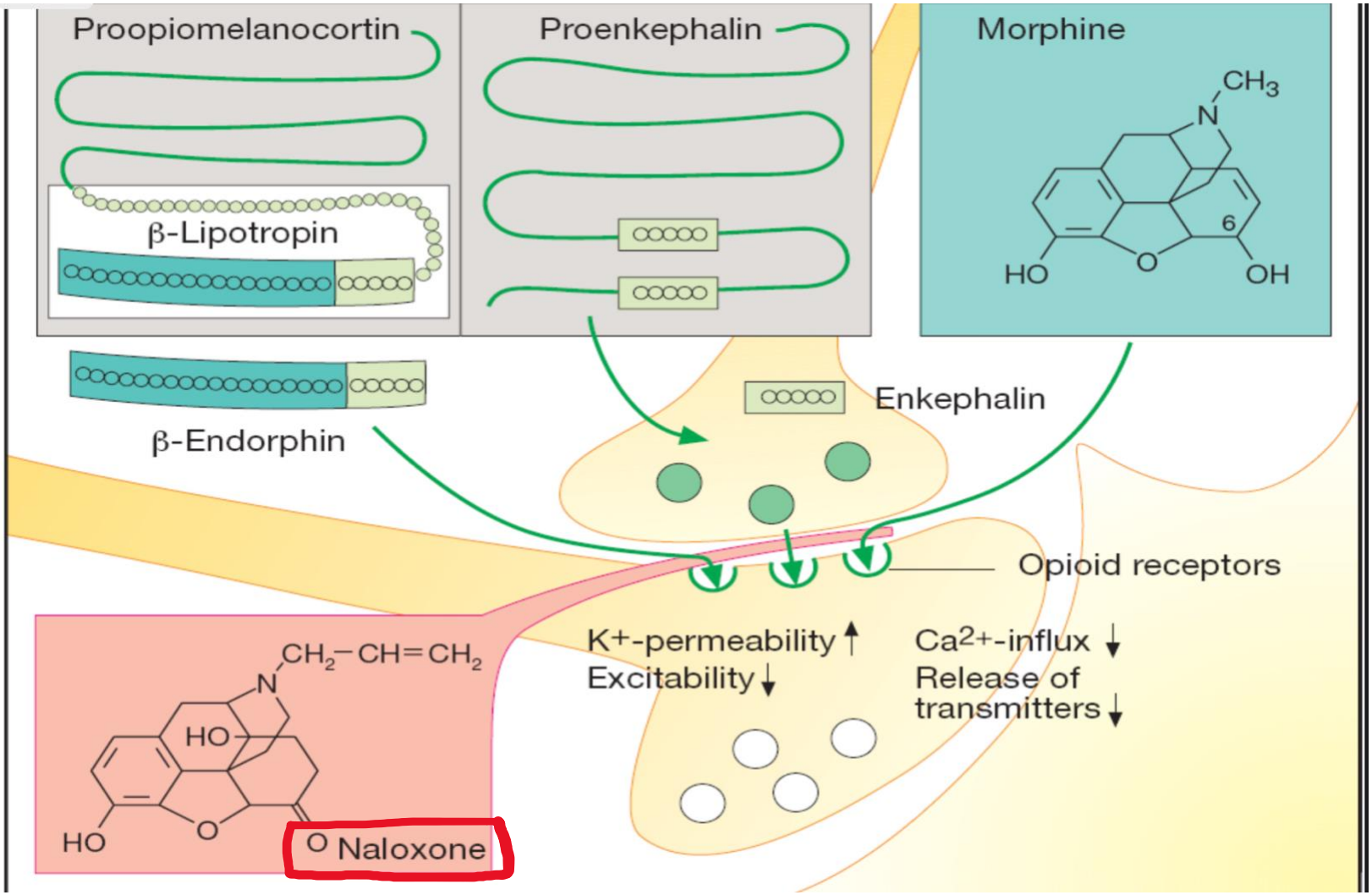
- Let's now talk about **Oxycodone** **which is the most prescribed opioid in US because it is believed that it's addiction liability less than morphine which isn't true (actually the euphoria in morphine is stronger than that in oxycodone but oxycodone produces the sufficient analgesia that we look for so it is preferred more than morphine in us)**
- It is an oral drug , taken 3 times per day instead of 4 in morphine

❖ **Fentanyl : semisynthetic (we modified it) so it is 100 times**

stronger(more potent) than morphine it has special characteristics (it work fast ,finish fast) which means it's effects start within minutes on the other hand morphine needs 30 min -1h to start working, we use fentanyl in theaters as analgesic along with anesthetic drug to let the patient wake up faster(half life is almost 55 mins, so the patient wakes up an hour max after the surgery) and we control it's amount during the operation so we can give him another dose if the HR raised (he feel the pain) and it works fast ,and the nauseating effect end rapidly with fentanyl so it is the drug of choice in theaters.

- Given as patches to cancer patients and transdermal patches with sustained release (not given orally), we give lower dose for elderly . No tablets are made due to potency and narrow therapeutic window.
- Because it is 100 more times potent so it can reach the overdose very simple and fast and the person die from respiratory depression

- Heroin is an old drug ,it is the worst of all opioids because it has the highest chance to be addicted than all drugs because the euphoria produced from heroin is the highest .


Proopiomelanocortin
β-Lipotropin
Proenkephalin
Morphine
CH3
N
6
HO
O
OH
β-Endorphin
Enkephalin
Opioid receptors
K+-permeability ↑
Excitability ↓
Ca2+-influx ↓
Release of transmitters ↓
CH2−CH=CH2
N
HO
HO
O
O Naloxone

- **The overdose of all opioids can be overcome by antagonist which is naloxone (antidote) which bind to opioid receptors .**
- **Mepiridine bind to muscarinic receptors so if it caused toxicity it won't be antagonized by naloxone**

(Mepiridine, pethidine)

- Repetitive dosing leads to accumulation of the toxic metabolite normeperidine (normeperidine)

- Norpethidine (fat soluble)accumulation causes
  - CNS hyper-excitability, subtle mood changes,

  Tremors, Multifocal myoclonus, Seizures

- Common with repeated large doses, eg 250 mg per day. Shouldn't be given for more than one week (3 days in the US)

- It is renally cleared, and use of meperidine in patients with kidney disease is not recommended .

Mepiridine(is drug of choice in:)

- Obstetric labor (it is the drug of choice in labor because it has the least stress on fetus)
- Shivering(because of hypothermia) which is a common situation after labor in 10% of ladies.
- It has less euphoric effect than morphine and less chance to be addicted
- It increases the release of serotonin in brain like antidepressant drugs so it is contraindicated in patients taking antidepressants.

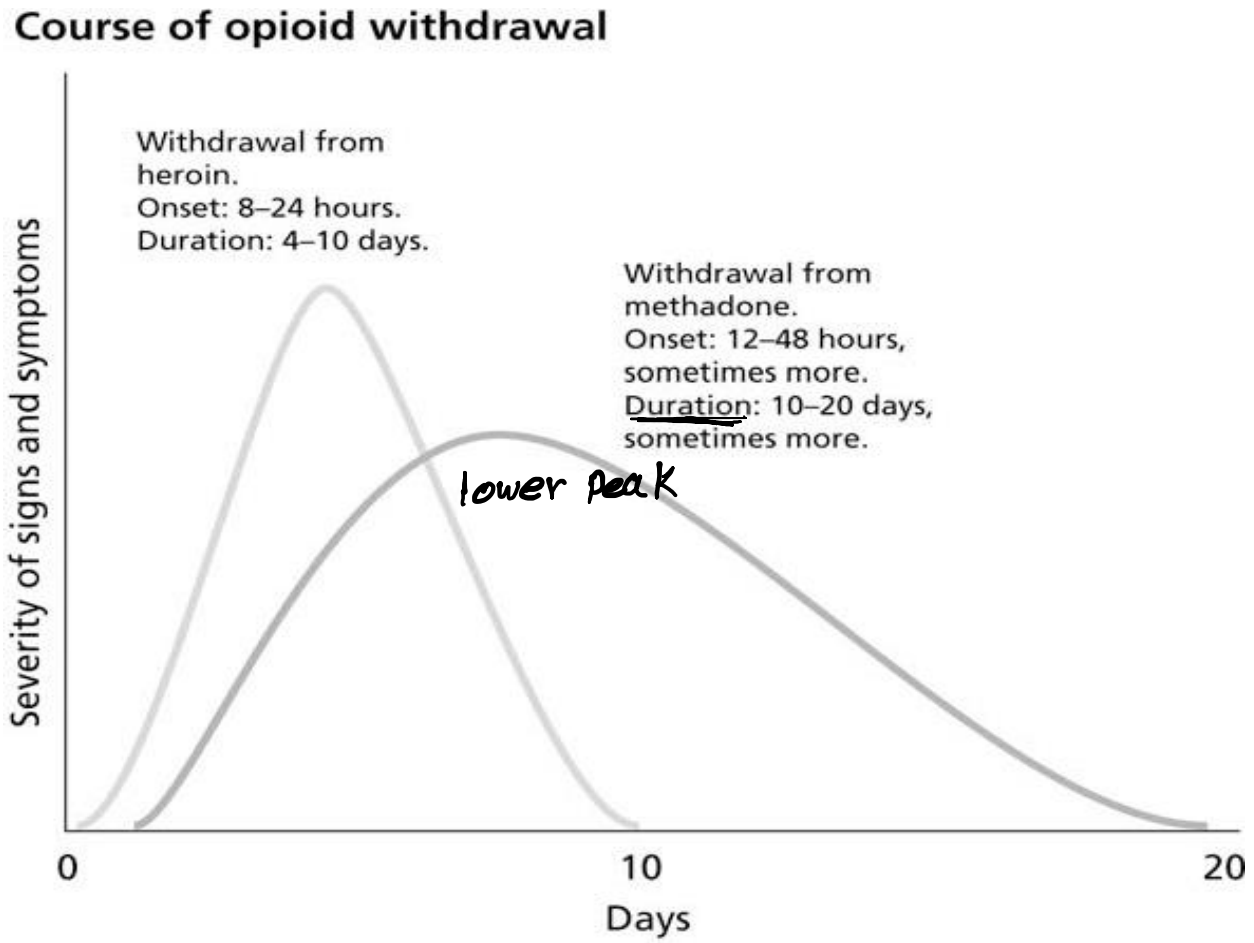
Methadone

- NMDA receptors blocking
- Monoaminergic reuptake transporters.
- Treat difficult to treat pain, especially when morphine failed.
- Widely used in opioids abuse.

why?????

- Methadone not used in treatment except for some purposes
- Methadone is the drug of choice in treating morphine and heroin addiction because it has long half life (at the beginning half life is 8h after week it can reach 36h because methadone has accumulative dose) and much less euphoric effect (half the effect of morphine)

- This slide compare between the half life and the activity of the drug between heroin and methadone (watch the lecture to understand min 28:00)



Tramadol

- **Partial agonist(on mu receptors), increases serotonin levels like mepiridine so they shouldn't be combined increases norepinephrine levels (called SNRIs: seretonin and epinephrine reuptake inhibitors)**
- **NEVER given with mepiridine or antidepressants --> serotonin syndrome**
- **intermediate analgesic effect so used for moderate pain**
  - Analgesic action mechanism
    - Not fully understood
    - Weak affinity for μ-opioid receptor
    - Inhibition of norepinephrine reuptake
      → α2-adrenoreceptor activation

→ act synergistically with tramadol's opioid receptor activation

→ analgesia

- Advantage
  - Less respirator-psychomotor recovery depression, nausea, vomiting, constipation
  - Rapid
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

- Codeine is pure partial agonist morphine receptor (mu receptor)
- Treat moderate-severe(not severe) pain (that's why it is weak opioid), works as an antitussive
- Less euphoria, less CNS depression, less variation and causes less problems with the elderly (geriatrics)
- It's commercial name is REVACOD.
- Treat toothache not responding to profen, simple muscle pain, التواء بالكاحل and migraine not responding to steroids
- Codeine is a prodrug metabolised by CYP2D6 , in our region there are 13.5% are ulta-rapid metabolizers(duplication at the level of gene), so they rapidly convert codeine to the active form (morphine) which is toxic for babies and cause seizures that's why codeine shouldn't be used postpartum (contraindicated) especially in our region again.
- Our region has a good number of ultra metabolizers, 28% of Ethiopians,

20% of Saudi Arabians, 13.5% of Jordanians, 8% in Turkey, and 6% of Spanish and Italian people unlike Sweden which has 0%, so must be very careful when serving this drug.