CNS
Doctor 2021

Pharmacology

Modified (2)

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Tolerance/Dependence/Addiction

- Tolerance

– Physiologic phenomenon resulting in progressive decline in potency of an opioid with continued use.

Dependence

– Physiologic state characterized by withdrawal symptoms upon abrupt discontinuation/ reduction of narcotic therapy.

- Abstinence syndrome
- Independent of tolerance

Addiction

– Psychological & behavioralsyndrome manifested by drug seeking behavior, loss of control o drug use, and continued us despite adverse effects.

In last lecture we talk about ; addiction , tolernace and dependence are completely different terms , you must sperate between them..
some drug causes addiction ,
some drug cause tolerance only and so on .
but in opioids we got all of them ..

Tolerance and Dependence

This picture shows a person who needs opioids , he is suffering from addiction ,tolorence , and dependence..

Morphine half life is 4 hours , so the biggest mistake is to stop the drug suddnly why?!

Because of withdrawal reactions..

Withdrawl Reactions

Acute Action <-Opposite ->	Withdrawl Sign
• Analgesia	• Pain and irritability
• Respiratory Depression	• Hyperventilation
• Euphoria	• Dysphoria and depression
• Relaxation and sleep	• Restlessness and insomnia
• Tranquilization	• Fearfulness Due to the norepinephrine (sympathetic will increase)
• Decreased blood pressure	• Increased blood pressure
• Constipation	• Diarrhea
• Pupillary constriction Pinpoint	• Pupillary dilation
• Hypothermia	• Hyperthermia
• Drying of secretions	• Lacrimation, runny nose
• Flushed and warm skin Release of Histamine	• Chilliness and “gooseflesh”

If we stop the opioids suddenly, the patient will have withdrawal symptoms

Because they pass through 4 half life so the symptoms will apper .. because he doesn't have morphine receptor in his body,-tolerance- no morphine, no analgesic activity.. No inhibtion activity

At the same time ,the norepinephrine will be firring

The symptoms will be maximise within 24 to 48 hours

In second day , the patient will be very dangerous ..

Note: the more potent the opioids —> the more withdrawal symptoms..

The shortest half life —> the more early and stronger the symptom ..

You need to deal with this situation.. opioid problems.. because lot of people suffer from it..

Pregnancy and elderly

- If acetaminophen is insufficient, opioids are considered
- acceptable during pregnancy provided they are given for a short duration.
- Chronic opioid use can result in fetal dependence, premature delivery and growth retardation.
- In elderly

Opioid analgesics have an increased likelihood of more profound adverse effects as well as prolonged durations of action. Therefore it is best not to select an opioid.

If it is necessary, reduced doses must be utilized.

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				
Partial agonists				
Codeine	Less efficacious than morphine	Like strong agonists weaker effects	Mild-moderate pain cough	Like strong agonists, toxicity dependent on genetic variation

Doctor loves this slide

It will come in exam

E max for weak opioids < Emax for strong

Opioids

Weak opioids

Partial agonist , antitussive , dental pain

- Codeine
- Tramadol

Strong opioids

Full agonist

- Oxycodone
- Morphine
- Methadone
- (Zombie) Fentanyl
- Mepiridine

Each one has different applications and different side effects..

They all have similar structure in chemistry , but have few differences:
Example :

Codine differs from morphine : in one mythle group ..

Never ever use any of these drugs in labor except mepiridine

Because it delays the labor + makes stress on the baby .. how?!
By contraction of the uterus and cervix ..

Fentanyl (Zombie 🧟‍♀️)

لانه كل سبع دقائق بيقتل واحد سموه zombie 🧟‍♀️
because hundreds time potent than morphine
Very toxic

Half life is short,,Very narrow therapeutic index

Transdermal patches &injection not found orally due to low bioavailability

In anaesthesia &we put analgesic drug “fentanyl “ ..

Why we don’t depend on analgesia of anaesthesia only?!
Because it will put him in unconscious state - stage four ..(coma)
intraoperational أهم استخدام اله بالحياة

Fentanyl gets metabolized by the liver and gets excreted in the bile (it doesn’t reach the kidneys)
So we could use it with kidney’s patients (if it’s chronic we use patches and if it’s acute we use injections)

Codeine

دواء 💊 شهير للاسنان اسمه revacod
معدود الحبات من قبل وزارة الصحة ورقته زهرية ...

orally codaine has bioavailability higher than morphine , in the body; part of it enter as a codine but other part enter as morphine (it is not the main mechanism) ,
The true mechanism by bind neurorecptor act as partial agonism
don’t reach respiratory depression

Cyp2D6 -(found in liver)-> this convert
condine into morphine ..

In normal cases we have this enzyme in little amount
But people who have multiple genes -Southern people -for this enzyme (more than 2) have rapid metabolize for codeine which will cause toxicity.

In ultra rapid metabolizer , It can cause respiratory depression due to increase morphine in the body of the child
(adults with rapid metabolism will not be affected)..
For this reason it’s contraindicated in children .👦

Northern people (7-8%) of them are poor metabolizer the effect of morphine which comes from codeine will be weak .

Oxycodone

Oxycodone (not found in Jordan) same as morphine you can find it as tablets - orally -

Analgesic.. for chronic severe pain ..

Dont use it except you really in need for it ..

Bc of the tolerance,dependence and addiction..

Morphine

Half life 4-6 hours ..

- **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**

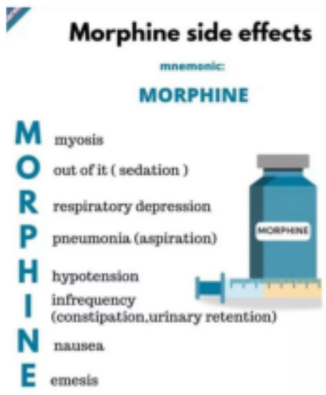
- **Morphine produce a powerful sense of euphoria and well-being.**

- **Morphine is also used in the treatment of acute pulmonary edema, intravenous morphine is dramatically relieve dyspnea cause by pulmonary edema associated with left ventricular failure.**

morphine causes hypotension, it opens precapillaries "connection between veins and arteries " so the blood will be pulled down , so it helps to pull the fluids in case of Plural effusion .

But we don't use it when patients suffer from bradycardia +plural effusion because the opioids stimulate the vagus nerve ..

Contraindications: in asthma
Hypotension



If the patient is in severe pain , example:

"مريض السرطان —>اذا بياخد جرعة على ١٠ الصبح و جرعته التانية على ٢ العصر
في حال زيادة الوجع خلال الفترة (١٠-٢)؟ بعطيه خمس او سدس الجرعة الي بوخدها من morphine ،، بس ماتعطيه نفس الجرعة لانه رح يصرله respiratory depression .. "

Morphine and mepiridine have same efficacy but potancy of morphine is Higher

Kidney

In patients who have renel problems we don't use Mepiridine and morphine

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

But morphine:

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. If the patient has renal insufficiency ,we don't give him morphine because the metabolites of morphine will accumulate which will cause toxicity to the brain

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,

Hydromorphone

- may be preferred over morphine for patients with decreased renal clearance, to preempt the potential for toxicity from morphine metabolite accumulation.

We use this drug if we don't have a -fentanyl drug-

Other name :

(Mepiridine, pethidine)

صُنع على اساس انه Atropine

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

So we dont use it for long time , because toxic metabolites accumulate ..

This is rate limiting factor of this drug
That why we dont use it longly ..

We dont use it in out patient because we shouldn't use it for more than 5 days

- Norpethidine accumulation causes
  - CNS hyper-excitability, subtle mood changes, Tremors, Multifocal myoclonus, Seizures

Why?
Due to serotonin and norepinephrine

- Common with repeated large doses, eg 250 mg per day.

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

Mepiridine

صُنع على اساس انه Atropine

Drug of choice in the labor , if the mother doesn't take epidural anaesthesia..

- Obstetric labor 🤱🤱 (Iv not orally)
- Shivering (Iv not orally)

After surgery some people (more in women)will have shivering ; we will treat them by mepiridine

It works by :
1-activition MU +GAPA +delta receptor
2- inhibtion of vagal nerve

Its a synthetic opioids ..
Anti muscarinic ,mu activitor ,

Mepiridine inhibits the vagus nerve (opposite to the rest of opioids) so the patient won't have the side effects related to vagus stimulation , the patient won't have any symptoms of constipation or bradycardia or myosis or urinary retention or hypotension.
So I could use mepiridine in prostate hypertrophy , gallstones patients and patients who suffer from bradycardia.

We can use them in asthmatic patients

- Mepiridine used for colic pain example : in case of diverticulitis because it doesn't have spastic effect (remember it doesn't stimulate the Vegas nerve)

Contraindications :
You shouldn't give the mepiridine with
1-SSRI (selective serotonin reuptake inhibitors)
2-MAO Inhibitors (inhibition of metabolism of the serotonin,norepinephrine)

Methadone

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

why?????

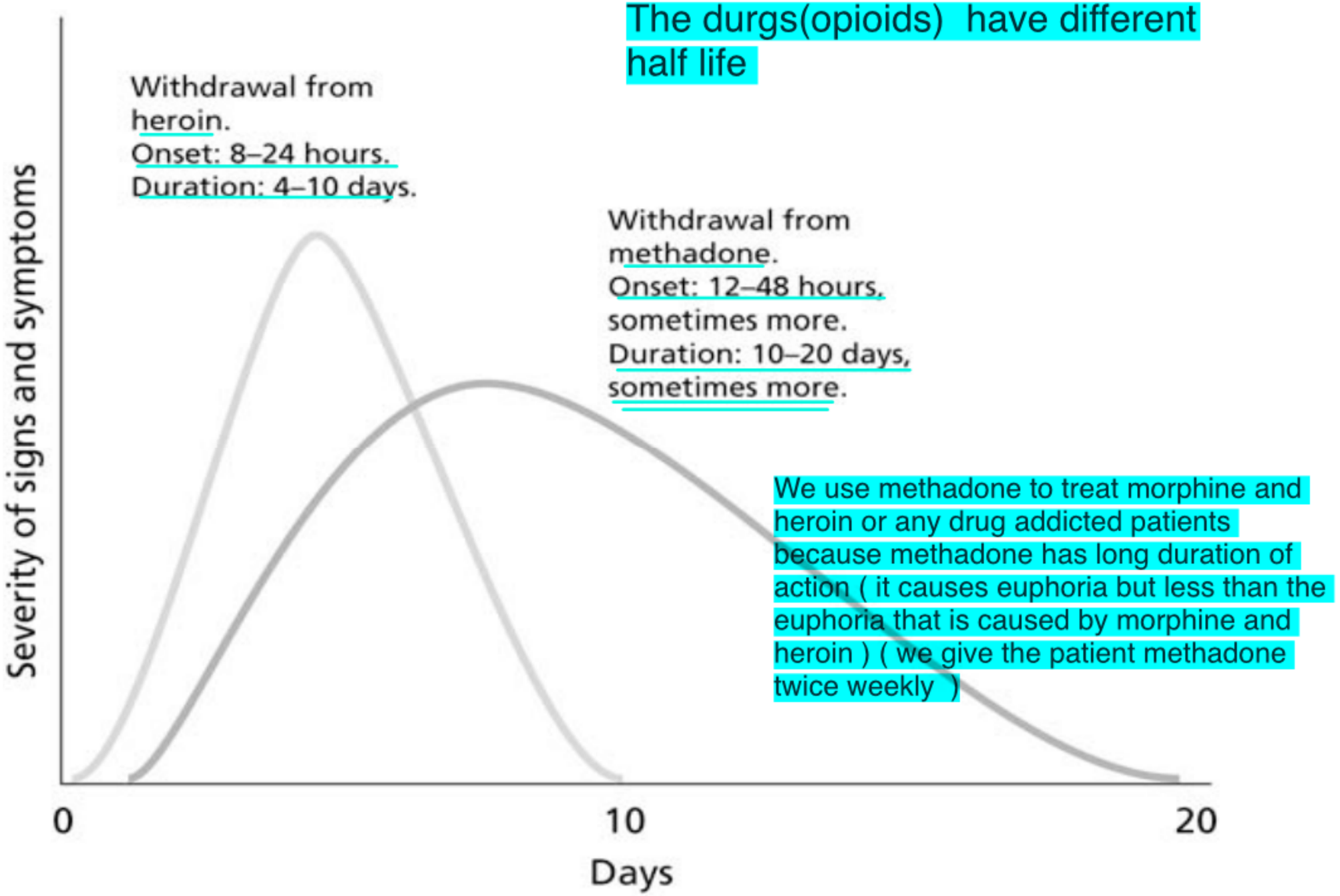
Also methadone blocks the NMDA receptors, its mechanism of action is different than morphine so we use it when patient develops tolerance (doesn't response to morphine) these process called : opioid rotation
For more clarification, opioid rotation means we give a drug which differ in structure and MOA such as when patient developed tolerance to morphine we use methadone (for month then we back to morphine)

How it cuase death?!

Methadone causing long QT interval (torsade de pointes) which causes death before respiratory depression occurs, each year 4000 patients die from methadone overdose in USA

Course of opioid withdrawal

The durgs(opioids) have different half life



We use methadone to treat morphine and heroin or any drug addicted patients because methadone has long duration of action (it causes euphoria but less than the euphoria that is caused by morphine and heroin) (we give the patient methadone twice weekly)

Source: NSW Department of Health (2007) NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines

Tramadol

Partial agonist
Orally or injection

- 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 respiratorpsychomotor recoveryy depression, nausea, vomiting, constipation
  - Rapid
- Moderate pain treatment : as effective as morphine
- Severe pain treatment : less effective than morphine

MOA: inhibition for norepinephrine re uptake and when it increases in the brain it causes feedback inhibition on a2 receptors causes inhibition on of norepinephrine outflow which causes analgesia.

clonidine have the same idea for pain management

You shouldn't give the tramadol with 1-SSRI (selective serotonin reuptake inhibitors) because it increases the norepinephrine, make a " serotonin syndrome "

Peripherally Acting Opioid→

- Opioid receptor – outside central nerve system
  - Peripherally acting opioid agonist
    → analgesia without CNS side effect
- Loperamide
  - μ-opioid receptor agonist
  - Not cross blood-brain barrier
  - Treatment : inflammation-induced hyperalgesia
  - Relieve diarrhea

اللهم انصر اهلنا في غزة ..

الحمدلله 💕

V2: Release of histamine