

## Pharmacology lecture 2

There are two different terms related to opioid treatment that must be well differentiated.

The first is *HYPERALGESIA*; which means **increased pain sensitivity** due to **sensitization** of **pronociceptive** mechanisms (i.e. the mechanisms that produce pain become more effective) and this phenomenon is associated with patients under chronic high opioid doses. These patients develop hypersensitivity towards both noxious and non-noxious stimuli.

The second is *TOLERANCE*; which means **desensitization** of **antinociceptive** mechanisms (i.e. the mechanisms that reduce pain become less effective).

It's really difficult and important to differentiate between these two terms clinically, because both tolerant and hyperalgesic patients will come to your clinic asking for increasing the opioid dose. Increasing the dose for a tolerant patient will be effective, while ineffective and in fact dangerous for a hyperalgesic patient.

Suggested mechanisms of hyperalgesia :

- 1- abnormal NMDA receptor activation.
- 2- long term potentiation.

**\*\*So what do we do to reduce hyperalgesia ?**

- NMDA antagonists.
- Opioid rotation ( rotating the patient between different opioid analgesics for example giving him hydrocodone , then oxycodone , followed by morphine , and so on.., this will reduce the probability of hyperalgesia or tolerance , and the reason is that each opioid has differential mechanism of action , which is activating different receptors in addition to  $\mu$ -opioid receptor , so the patient's CNS will tolerate this type of opioid for example morphine which is pure  $\mu$  receptor agonist, and then we disturb this tolerance by introducing another type of opioid that has another mechanism of action).
- Methadone (this drug acts as both NMDA receptor antagonist , and opioid analgesic).

#Studies showed that patients getting chronic opioid treatment under medical observation won't suffer from hyperalgesia. Over activation of opioid receptors will lead to respiratory depression, to put the patient away from this risk you need to antagonize the treatment by giving an antidote. Just as there is opioid receptor activator (Enkephalins and Endorphins), there is an **opioid antidote (Naloxone)**.

## OPIOIDS

Strong Opioids
<ul style="list-style-type: none"><li>• Oxycodone</li><li>• Morphine</li><li>• Methadone</li><li>• Fentanyl</li><li>• Mepiridine</li></ul>

Weak Opioids
<ul style="list-style-type: none"><li>• Codeine</li><li>• Tramadol</li></ul>

They are common drugs, they don't have ceiling effect unlike NSAIDs. ( Ceiling effect : increase in dose does not increase analgesia but increases side effect)

So when a patient comes to the hospital with severe pain, you need to give him an opioid and keep a close eye on him, because of opioids' side effects: nausea, vomiting, constipation, respiratory depression, CNS depression, euphoria, itching, urinary itching, .... So you have to balance between the risks and benefits of the drug.

### 1- Morphine

\*oldest drug , used to relief severe pain (analgesia).

Morphine uses:

**\*preanesthesia before surgery.**

we use anesthesia during surgery so why do we use morphine ?

because increasing anesthesia dosage increases mortality rate, so one way to reduce the anesthetic dose is to use an adjuvant drug (one example on an adjuvant drugs is opioid)

\***severe pain** ( cancer , post open heart surgery ,...) the patient won't respond to normal analgesics so we give opioids

\***sedative activity**: 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 (this is one of morphine benefits but don't ever think of using it as antidiarrheal drug)

**(again don't ever use morphine for its euphoria effect)**

\* Morphine is also used in the **treatment of acute pulmonary edema**, **intravenous** morphine dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure. (the reason of giving morphine in such case is because of its anxiolytic effect, and so it reduces dyspnea).

\*In kidney failure patients, but here metabolites might built up so we should either reduce the dose or monitor our patient. OR there is another drug called **hydromorphone**, it's a derivative of morphine and has a similar activity, but doesn't produce morphine's high metabolites problems (myoclonus , and confusion) , explanation on this point from the slides →

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.

BOTTOM LINE : we use morphine for acute pulmonary edema (dyspnea), analgesia for severe pain, preanesthesia, postoperation for sedation. *We never use morphine as antidiarrheal drug or for euphoria.*

## 2-pethidine

\*mainly used in obstetric labor

Why is it used in obstetrics only and can't be given repetitively (given only once or twice) ?

1-repetitive dosing leads to accumulation of the toxic metabolite normeperidine

2-norpethidine accumulation causes:

CNS hyper-excitability, subtle mood changes, tremors, multifocal myoclonus, seizures.

3-its renally cleared, and usage of meperidine in patients with kidney disease is not recommended.

\*\*these effects are common with repeated large doses, eg 250 mg per day (as a doctor you're not allowed to use this drug repetitively, given only once or twice per day).

Uses of pethidine :

1-obstetric labor: opioids in general cannot be used in this case because they might cause respiratory depression in fetus. however, pethidine is an exception so it's considered the drug of choice.

2-shivering: the main cause of shivering in hospitals is postanesthesia, that's because the patient is under CNS depressants affect which will cause disturbances and malfunctioning of the temperature centers. We relieve the shivering of a patient by either keeping him warm or administering some drugs such as pethidine.

### 3-Methadone

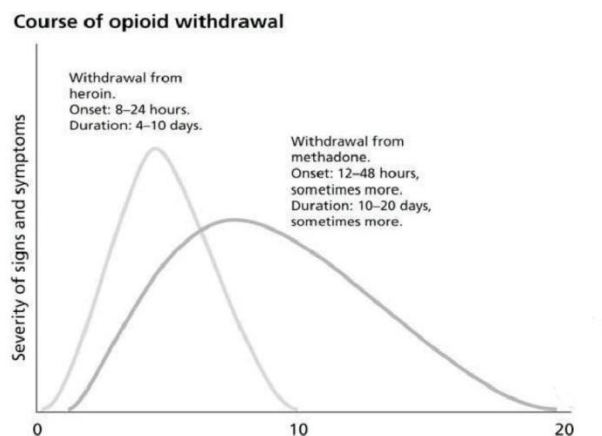
\*It has a dual activity a)  $\mu$  receptors agonist b)NMDA receptors blocking agent

\*we noticed alot of death cases due to addiction towards it.

USES:

1-used to treat difficult cases of pain, especially cases where morphine failed to relief pain (when  $\mu$  receptor agonist isn't working(morphine) we have to use another mechanism which is NMDA receptors antagonists (methadone))

Ex.it's used to relieve neuropathic pain that doesn't respond to morphine .



2-widely used when opioids are abused:

Methadone is a drug similar to heroin, although it lasts a lot longer in the body. It can be prescribed. If you take methadone, withdrawal symptoms are much less severe. We can notice the difference in the withdrawal symptoms severity by checking both curves in the figure above.

If you stop taking heroin, methadone can prevent or reduce the unpleasant withdrawal symptoms. People gradually reduce the dose and come off drugs altogether it might take up to 6 months.**(withdrawal signs of methadone are relatively less severe)**