

# Pain

Our topic today is about analgesics.

**General concept:** pain brings patients to the Doctors at the same time. Fear from the pain can keep the patient from going to the Doctors at appropriate time.

We don't go to the dentist because we are afraid from him and his tools for example.

Treatments are often done on the inflamed, hypersensitive tissues of a patient, very important when it is related to operations.

Pain is a symptom of a pathologic condition that needs to be taken care of :-

– If no treatment, still pain.

– It is Induced by the release of histamine, serotonin, prostaglandins, bradykinins ,etc that activate pain signaling.

Prostaglandins main activity is toward the peripheral more than the central system.

We are going to deal with the central nervous system to treat the pain not the inflammation.

Note: inflammation is always linked with prostaglandins.

## Terms and Definitions

- Analgesics: drugs used to relieve pain. This derives from Greek an-, "without", and -algia,:"pain".

Analgesic drugs act in various ways on the peripheral and central nervous systems; they include the non steroidal anti-inflammatory drugs (NSAIDs) and opioids.

- Anti-inflammatory: property of a substance or treatment that reduces inflammation.
- Anti-pyretic: Prevents or reduces fever by lowering the body temperature from a raised state by acting on the hypothalamus. Will not affect the normal body temperature.

- Addiction: Dependence on a substance (alcohol, drugs) to the point that stopping is very difficult and causes severe physical and mental reactions.

one of the main problem in the world is addiction mostly for alcohol and smoking (nicotine).

Addiction toward opioids ( almo5addarat ) is a really big issue but it is not a very common problem because it is not justified ( because in west most of people drinks , including the people who works in writing books or media so they say : moderate drinking is not bad , so it becomes socially accepted ).

However no one can say that opioids have a good activity.

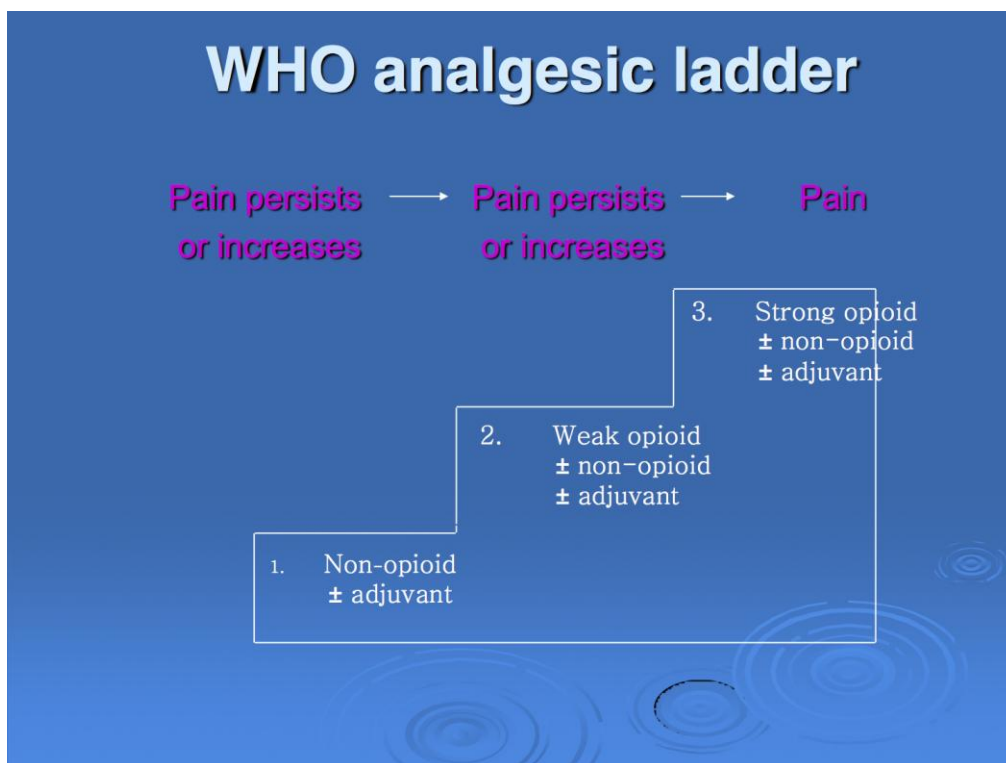
It is also depends on regulations.

In Jordan we have a good regulation however not that great.

## Pain types

You have to evaluate the patient's pain in order to choose the appropriate pain killer, so you have to understand that pain has many levels; mild , moderate and severe pain.

So if you are dealing with mild to moderate pain then you are giving your patient a non opioid drug like non steroidal anti-inflammatory drugs with adjuvant, if the pain is more severe and persist then you move to weak opioids with or without non opioid drug, if it is extremely severe then you have to give your patient a strong opioid drugs.



## Non-steroidal anti-inflammatory drugs (NSAIDs) Mild to moderate pain

**Background:** previously in the musculoskeletal system we have taken the non steroidal anti-inflammatory drugs such as Ibuprofen and voltaren which deals with the normal pain such as headache neck pain tooth pain etc.

### mechanism of action

Non steroidal anti-inflammatory drugs inhibits cyclooxygenases ; COX1 and COX2 , they inhibit the synthesis of prostaglandin which are pain mediators.

So when I inhibit those pain mediator I reduce the pain.

There are selective drugs for inhibiting COX2 which is the one who is related to inflammation, since COX1 has a roll in gastric protection, so by selective inhibition to COX2 I target the inflammation only without losing the protective facility from COX1.

Note : Ibuprofen and aspirin are COX non selective (both 1 and 2) inhibitors , so it must be taken after meals (full stomach) , because of COX1 inhibition effect on empty stomach.

Celecoxib : is a COX2 selective inhibitor , we prescribe it for patient with peptic ulcer.

### Usage

Mild to moderate pain could be treated by NSAID.

Those drugs are only used for mild to moderate pain why?  
Because those drugs have **low ceiling** (sa8ef) EFFECT.

Low ceiling effect: means that increasing the dose will increase the effect **UNTILL** you reach a point that increasing the dose will have no effect (those drugs have a certain limit), or in another words: most of the drugs have an (E MAX) Which is related to the efficacy, the (E max) efficacy of those drugs are relatively low (so used in mild to moderate pain).

So those drugs can't control the severe pain such in cancer patients, even if you increase the dose (you will increase the dose for nothing).

## Opioids

Severe Pain, examples: neuropathic pain, cancer pain, during operation and post operation pain are all severe pain , most of those are mediated by CNS.

Here in severe pain we will deal with it in different way than mild to moderate pain how?  
مخدرات by the Opioids ( pain big gunners )  
الكلمة لحالها بتخوف :P

Prescription of those drugs is a serious issue, you can't have them without prescription, you can't buy them from everywhere, they even have a special prescription paper (pink in color).

So it's really serious why?

Because by miss-using it, you may kill your patient, or even you as a doctor or a pharmacist or anyone has an access to have it may become addicted if he use it , so those drugs must be protected from abuse.

Another reason the therapeutic window for those drugs are relatively narrow, how is that?

Because they may cause a respiratory depression, in high dose the oxygen receptors they will be off, so that may kill the patient.

Those drugs also cause pupil myosis (pinball pupil).

So whenever you hear about an addictive person has been killed after drug (heroin) overdose you must know that he was killed by a respiratory depression, and if you look at his eye you will notice that his eye pupil is constricted.

Addiction is a serious problem in west.

## Opioid analgesics

All drugs in this category act by binding to specific Opioid receptors in CNS to produce effects that mimic the action of naturally occurring substances, called endogenous opioid peptides or endorphins, or enkephalins.

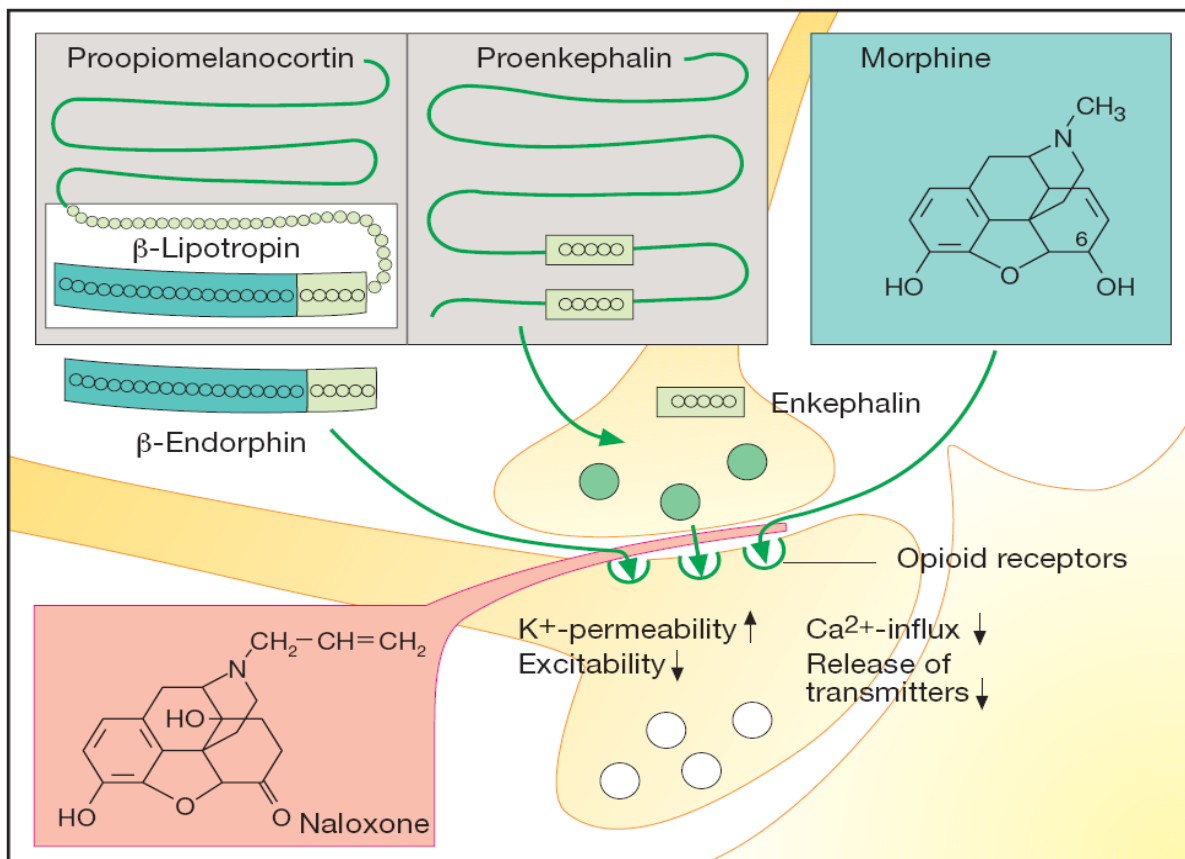
Opioid receptors:

mu , gamma and delta.

We really care in pharmacology on mu receptors the other receptor types are just an adjuvants (they help in the activity of opioids), or they may have effects but we don't know them.

However we only concerned about the mu receptors.

## Mechanism of action



depending on the graph above :-

### How opioids Work

Physiologically the endogenous substances Endorphins and Enkephalins bind the mu receptors to induce two actions :-

- 1- they close the Calcium ions channels.
- 2- they open the Potassium ions channels.

So they inhibit the activators and activate the inhibitors of releasing the transmitters such as substance P -which mediates the pain in CNS-, bradykinin , serotonin ,and norepinephrine  
The most important ones are: substance P and bradykinin.

So I am pushing the patient toward the depressed situation, that the activity in the CNS will be reduced.

Endorphin and enkephalins works more selectively than the drugs, they are induced under cases such traumas, they really block the pain but they don't induce side effects due to their selectivity however using opioids drugs inhibits the pain however. They will also inhibit many another things to induce many side effects.

However the exact mechanism that makes the endogenous mediators more selective and don't induce side effects is not really known.

## Opioids Antidote

Naloxone is the antagonist for the opioid mu receptors.  
It's mostly selective to mu receptors.

Note : respiratory depression is a common issue , why?

Because many times you reach a condition that you can't deal with the pain (your patient is suffering from a pain and you have to cure him and the only way to deal with this pain is to give opioids why?

Because opioids **does not have a ceiling activity**, so as you increase the dose, you are getting more effect until endless.

Remember NSAID's have a ceiling activity.

Even that opioids have no ceiling effect, but it has a limiting factor that prevents you from increasing the dose.

This limiting factor is the respiratory depression.

So if your patient had a respiratory depression you have to stop the opioid dose and then you have to give him the antidote, which is Naloxone, so you rescue your patient.

Naloxone is antidote for all opioids.

# Opioids effects

Physiologically opioids have two effects; Stimulant effects and Dampening effects.

## **Dampening (reducing) effects :-**

- 1- we reduce Pain (Analgesia) ; the desired effect.
- 2- we reduce mood alertness; it is advantage during surgery when the patient is anxious and worry about everything happens around him, so **we reduce the Anxiety.**
- 3- reduce Respiratory center activity.
- 4- reduce Cough center activity (Antitussive).

Note : the doctor mention that ; the only Antitussive which really has a real Antitussive activity is codeine (Revacod) , it's only sold on two pharmacies in Jordan.

## **Stimulant effects :-**

- 1- Analgesia of opioids comes from two activities: Activation of inhibition (Dampening effect) and inhibition of activation.
- 2- Antidiarrheal; most of the patient that take opioids become constipated.

# Opioid Analgesics Side Effects

The main mechanism for the side effects, that many tissues in the body have the mu receptors other than the target.  
so opioids are not only selective for the desired receptors that blocks pain.

## **The side effects :-**

**1- Euphoria** : who use opioids will feel very satisfied and Happy , however it's a side effect , because whenever the patient take the drug he will become Euphoric and he will be addicted to have the same feeling.

Why it happens?

Because there are mu receptors in the reward centers in the brain, so opioids will stimulate those centers.

**2- CNS depression:** because you inhibit the excitation and excite the inhibition you will get CNS depression.

respiratory depression is linked with euphoria, that the more you CNS is depressed the more euphoric the patient is.

when the addictive people take euphoric drugs like lorazepam (9aleeba). They drink alcohol with it, that the alcohol will induce more CNS depression and as we said it's linked with euphoria so the addictive will be more euphoric.

- 3- Nausea and vomiting: Nausea and vomiting centers will be targeted.
- 4- Respiratory depression.
- 5- Urinary retention.
- 6- Diaphoresis and flushing.
- 7- Pupil constriction (miosis) : this side effect will not be tolerated.
- 8- Constipation: this side effect will not be tolerated.
- 9- Itching.

## **Repeated use of opioids (Morphine)**

Morphine : is one of the oldest drug , by using morphine and aspirin pharmacology came out and before that it was only herbal medicine.

**Effects:** it's a magic drug, best analgesic , without a ceiling effect.

However Repeated use of morphine will cause :-

### **1- Tolerance :-**

As you use the drug chronically the patient become less responsive toward the drug.

What are the effects that will be tolerated ?

- 1- Euphoria it will be tolerated so patient with the time will ask for more dose or stronger drugs.
- 2- CNS depression it will be tolerated.
- 3- all of the effects and side effects of opioids will be tolerated **except:**
  - a- Pinball pupil
  - b- Constipation

### **2- physical dependence :-**

The patient who chronically takes the drug will have a change in his body and when withdraw the drug the signs will appear.

Example when you give a patient a beta-blocker the body will increase the number of receptors, and when you withdraw the drug the patient will have hypertension crises.

Another example smoking: when the patient smoke for long time, something in his CNS and the body changes, so when he withdraw smoking he will get effects like becoming fatter and more angry etc.

When the patient takes opioid: there will be activation of receptors, and when the receptors are activated many times repeatedly that will induce endocytosis for the receptors toward the cell, so the number of expressed receptors will be less so you the body will need more opioid to induce the same previous effect.

\* The receptor will be down regulated.

### **3- psychological dependence :-**

psychological dependence it is really an important issue to understand it read

this example :

When a student used to smoke withdraw smoking, and after one year he had a bad situation, having a bad exam for example, after this situation the first thing that comes to this student's mind is smoking, so he will get back to smoking.

Opioids apply the same concept however it is much stronger , addictive person are extremely lost.

Note : in such case this person is not physically dependence (the receptors are normal) , but he is psychologically (something related to his behavior).

#### **4- withdrawal :-**

When you withdraw the opioid you will have an opposite effects of the opioid effects why?

Because as we said the expressed receptors after using opioids will become less, however during using opioid those receptor even if they low they are activated by the drug presence, whenever you withdraw the drug you will be in a case that the number of the receptors are low and are less activated, so you will have the opposite effects of that when the receptors are activated.

Withdrawal reaction is related with physical dependence.

How to deal with this issue ?

By tapering the drug (withdraw it gradually), so that will give chance to the receptors to get expressed back to normal state.

## **Withdrawl Reactions**

### **Acute Action**

- Analgesia
- Respiratory Depression
- Euphoria
- Relaxation and sleep
- Tranquilization
- Decreased blood pressure
- Constipation
- Pupillary constriction
- Hypothermia
- Drying of secretions
- Flushed and warm skin

### **Withdrawl Sign**

- Pain and irritability
- Hyperventilation
- Dysphoria and depression
- Restlessness and insomnia
- Fearfulness
- Increased blood pressure
- Diarrhea
- Pupillary dilation
- Hyperthermia
- Lacrimation, runny nose
- Chilliness and "gooseflesh"

Note how withdrawal effects are opposite to the effect of opioids.

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