Opioids

We should know that opioids are different classes and categories , you should know that morphine is the most potent and most efficacious. We talked about methadone, fentanyl, hydromorphine.
What is the difference between morphine and hydromorphine ?
They are the same now, but before that we used to have differences such as that hydromorphine was only given IV, where morphine used to be given orally and this is sometimes written in books but nowadays they are the same both are given either IV or orally.
Why we use morphine?
Because of experience and due to that it is the parent drug of opioids, we use it in many cases.

Opioids till now:

-Morphine: the most efficacious or potent opioid
-Hydromorphine: is similar to morphine

-Pethidine: has similar activity, but has a problem with the building up of toxic metabolites, we don't use it for a long period we only use it shortly, in cases of obstructive labor and shivering as clinical application .

-Methadone : good drug, acting on μ receptors and NMDA receptors (they are glutamate receptors), they have long and nice but not nice :P withdrawal symptoms that means that these symptoms are less severe than heroin withdrawal symptoms
and we use it when we are rotating the opioids as we are introducing different mechanism of action, why ?
When we don't want the patient to become tolerant toward opioids .

Tramadol:

Today we'll talk about Tramadol, it is an everyday drug that is seen even at home. it is used mainly IV and can be prescribed orally, we should know that it is a weak opioid along with codeine.

Mechanism of action:

It is really not fully understood, it has a special issue, it is a modest μ receptor agonist or (let's say a partial agonist as codeine), but also it has another activity which is inhibition of NE reuptake and a serotonin releasing agent, this means more serotonin and NE in the synapse and this give us a good mood.

If we want to treat depression we increase serotonin or epinephrine and this give a good mood

Clinical app. :

In moderate to severe pain Tramadol is just as effective as morphine, such as a diabetic foot or fibromyalgia, and for let's say **neuropathic pain**, here we use Tramadol.

Fibromyalgia: it is a muscle weakness affecting all the body, like the fatigue syndrome, it affects females more than males mainly in age between 20-40, we use tramadol against it in cases where NSAIDs won't work

Why do we prefer it to morphine in moderate pain? **(advantages of the drug)**
1- because it has an intermediate side effect profile, less respiratory depression, less nausea and vomiting and less constipation.
2- Rapid psychomotor recovery, that is because the depression for the CNS is not widespread (whereas other opioids depress the whole CNS including the resp. center) so the patient will recover quickly.

Disadvantages :

1- It can't treat severe pain, because it has a ceiling effect, so we prefer to use a full μ agonist which is morphine not tramadol.
2- Withdrawal symptoms are really bad even worse than heroine withdrawal symptoms, because the tolerance will develop at two levels**, μ receptors agonism and increase in the NE and serotonin in the CNS**, so we have to make sure that our patient won't get addicted to tramadol .
Note: it is only addictive in high doses, the usual analgesic dose doesn't have euphoric activity, but as the dose increases, ST increases and addiction occurs, withdrawal after addiction is very difficult.
3- There is another problem here in Jordan is that tramadol can be obtained easily, and more frequently (doesn't need the pink prescription) and that's why we have more addiction for it between our patients, why it can be obtained easily ?
Briefly, we categorize opioids according to their riskiness into three categories the first one include heroin, the second include morphine and the third include tramadol, so it isn't considered a dangerous drug .

Oxycodone:

Similar to morphine and hydromorphine, but it is a weaker agonist than them, it is not important and we will not see it a lot.

Fentanyl:

Mechanism of action :

100x more potent than morphine, but not more efficacious than morphine, so we reduce the dose, from 5mgram of morphine to(0. 2)mgram of fentanyl, this isn't our concern as doctors, what really should be our concern is the effect not the dose.

It works fast , and finishes fast.

Works fast means, it's absorption and distribution is high, penetration in the CNS is very fast and the analgesic effect is very fast .
Finish fast means that it's elimination is very fast.

Clinical app.:

So it works fast finish fast
which means it is an emergency drug, when we use it ?

1- Sometimes during anesthesia, the patient may feel the pain we are causing him, so we need to give him an analgesic that works quickly: we give him IV fentanyl, it will work within 5-10 minutes, so the inter-surgery drug of choice is fentanyl .
Why do I need the drug to finish its effects quickly ?
So the patient won't suffer from more CNS depression after the operation, which he is already suffering from due to anesthesia and we want the patient to wake up quickly after.
Why we don't use morphine ?
because the time for onset of action is long, and I have to wait for about an hour to continue, also it is a long acting drug so its effect will last for 3 to 4 hours and this will cause more CNS depression to the patient.
Morphine is given before the operation, and if the analgesic effect gets reduced during the operation we give fentanyl .

2- In short endoscopy or catheterization where the whole procedure will need only half an hour so there is no need to use morphine instead we use IV fentanyl .

3- Its elimination is very fast, therefore it's not suitable for oral treatment, but in the US it is available as patches for generalized sustained release for about 72 hours (similar to nicotine patches). This is given for some cancer patients instead of giving morphine every 8 hours.

We can also find it as: lozenges, buccal spray and intranasal for children .

Codeine :

Mechanism of action :

partial agonist of μ receptors , weak opioid.

Clinical app :

1- Main activity is an antitussive agent (anti-cough drug)

Refacod is an antitussive drug, which is found only in two pharmacies in Jordan .

2- In dental pain where the NSAIDs don't work .

we can use tramadol or codeine but codeine is more effective than tramadol in dental pain .

Loperomide :

Mechanism of action :

Targeting peripheral μ receptors, outside the CNS, mainly in the GI tract and don't cross the blood brain barrier.

Clinical app. :

- Relieving diarrhea, most active drug against diarrhea.

Do we need to intervene in diarrhea ?

Yes, especially in elderly where they have idiopathic diarrhea for 2 weeks so we use this drug.

No side effect, except water retention in cases of hyperplasia of prostate.

Note:

We should know how to use opioids with two important groups of patients :

1-Pregnant women :

we are ALLOWED to use opioids with pregnant women if they have severe pain and acetaminophen and the NSAIDs are not working or are contraindicated. But **not** chronically, because the chronic use will results in fetal dependence, premature delivery and growth retardation.

2- Elderly :

They have what we call delirium, and their CNS is really down due to their old age,
so they are more prone to the side effects of the opioids, they are really more responsive for the opioids and the opioids will have a prolonged effect
as the opioids are making somehow a synergistic effect on them .
We use opioids with elderly people who really needs **opioids but we have to titrate the dose .**

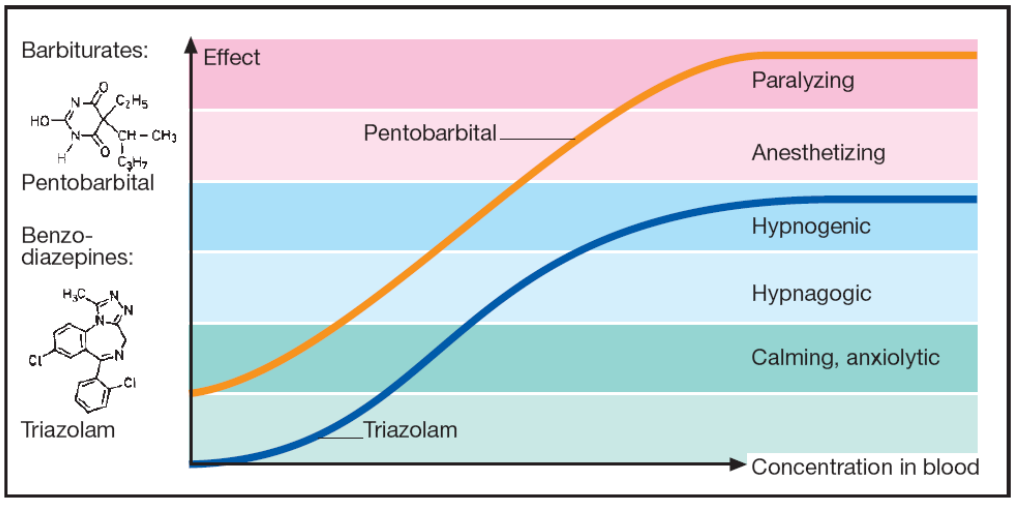
Anxiolytic and Hypnotic drugs

Anxiety : means stress and has the same signs as the sympathetic activation (tachycardia, palpitations etc..)
Hypnosis : induction of sleep.

We all know that life events always cause stress for people, and it is common with medical students and doctors except Dr.Malek as he said that he is always smiling. This daily stress isn't the stress that should be targeted by anxiolytic and hypnotic drugs, so as a doctor you shouldn't prescribe or use these drugs except you feel that the stress is a pathological one, because the drugs have adverse effects of tolerance, dependence and withdrawal symptoms.
In Jordan we have the problem of uncontrolled selling of these drugs, because pharmacists sell these drugs without prescription, on the other hand the ministry of health don't allow the drugs to be sold except with prescription but they aren't really serious in restrictions toward these drugs and In order to control this they should put more restriction on these drugs.

General mechanism of action :

These drugs have calming or depressing effect on the CNS by modulating the GABA A receptors that are found on the Cl^- channels, binding of GABA to its receptors causes their opening, which will have an inhibitory effect on the CNS and will lead to depression of the CNS .
The same drugs are used for anti-anxiety and hypnosis but they differ in the dose, so at low doses we produce an anxiolytic or calming effect and at higher dose we will have hypnagogic (sedative) effect, and if we increase the dose more we will have a hypnotic effect.
check the figure below



C. Concentration dependence of barbiturate and benzodiazepine effects

What are these drugs ?

1- Barbiturates: throw them, we don't need them anymore, because of their narrow therapeutic index .

2- Benzodiazepines (diazepam, or what is called valium):

they are the most used drugs.

3- Z-drugs: they are new hypnotic drugs, they were introduced in 2008.

Benzodiazepines:

The most common anxiolytic and hypnotic drugs, they replaced barbiturates because they <u>are safer and more effective .</u>

They are three categories :

1-Short acting : works for 2-3 hours.

2- Intermediate acting: works for 6 hours.

3-Long acting: work for more than 12 hours, such as diazepam

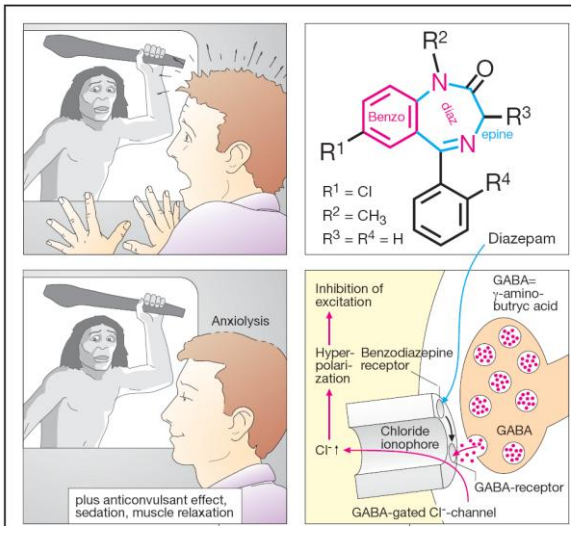
Mechanism of action:

They bind to GABA A receptors' allosteric sites which are called benzodiazepines allosteric or binding site, when BDZ bind to them **<u>they increase the frequency of the Cl^- channels opening and so we call them allosteric agonists. (GABA A receptors are bound to chloride</u>** channels).

More Cl^- in → hyperpolarization of the postsynaptic neuron → keep the cell away from firing an action potential, **<u>by simple words you are activating the inhibition .</u>**

They differ from the barbiturates where they prolong the time of opening of the channel not the frequency, their binding site is distinct from that of benzodiazepines.

There is a disease called panic disorder and we use benzodiazepines to reduce the anxiety that is caused by this disorder and the patient will relax, as in the picture .



Clinical app. :

1-Anxiety :

Failing in an exam,"2nd year was really hard and stressful".
This type of stress is really a normal daily stress and you shouldn't prescribe the drug for it .

It <u>not</u> used for daily stresses only for severe pathological anxiety.

Even if you prescribed them, they shouldn't be given for more than 2 weeks, not for long time due to their addiction potential, which is not related to euphoria.

* Addiction, will happen due to these reasons:

a) How you will convince the patient to stop the drug that relieved him from his anxiety and stress.
B) The withdrawal symptoms-which are the opposite effects of the drug- here the anxiety will come back as a withdrawal symptom, so the patient will think that it is the same anxiety that we targeted but really it is different .

* If the treatment is for a long period: we should use a longer acting drug, to cover the patient for long time. Whereas if we use short acting drugs, we will need to dose the patient a lot and this will cause fluctuation of the drug inside the patient's CNS , and this fluctuation will cause tolerance .

*The anti-anxiety effects of the Benzodiazepines are less subject to tolerance than the sedative and hypnotic effects, because we dose the patient with small amounts the will cause only anxiolytic effect, refer to the first diagram.

*What is tolerance?

Decreased responsiveness to repeated doses of drug-occur when used for more than one to two weeks. So if it is used for more than 2 weeks we will have what is called cross tolerance, which is associated with a <u>decrease in GABA receptors density</u>, this means that the number of receptors that are available for the drug will decrease and the effect of the drug will be reduced.

2- Muscle relaxant:

At high doses we will increase the presynaptic inhibition in the spinal cord and this is used to relax muscle strain and spasticity. We use diazepam centrally to treat muscle spasms occurring from muscle strain and in treating muscle spasticity from degenerative diseases such as MS (multiple sclerosis), but it isn't the drug of choice.

<u>The DOC is **Baclofen** that works on GABA b receptors and it inhibits the release of Ca++ , not centrally acting</u>.

3- Sedation and hypnosis :

Increase the dose, instead of 10mgram of valium we give 25-30mgram for example. What we should know that we have to increase the dose.

Where to use:

1-In hospitals:

a) premedication in surgeries with morphine

b) post operational if the patient has high anxiety and we want him to sleep .

2-In community:

insomnia is a really big problem in the western world, where 1 out of 5 people can't sleep, we have this problem in Jordan problem but to a lesser extent.

Hypnotic drugs are the most prescribed drugs on this planet, with high doses, this isn't right but we have to solve the issue of sleeping, because to be deprived of sleeping means increase in the stress and the irritability, the immunity will be decreased and the patient will be more susceptible for infections, exacerbate the symptoms of diabetes or hypertension etc…

so we have to deal with this problem.

*It is important to balance the sedative effect needed at bedtime with the residual sedation hangover on awakening, which means that we should include the duration of action in our calculations, and to prevent the patient to stay under the sedative effect of the drug after he wakes up.

This remind us of the alcoholic sedative effect and the hangover on waking up that it causes.

In the treatment of insomnia we have also to consider the pattern of difficulty of sleeping , some have problem in initiating the sleep, others have fluctuations so they sleep for 1 or 2 hours then wake up and so on (intermittent sleep) and others only sleep for 4 to 5 hours and then wale up so we need to prolong their sleep.

That's why we use drugs with different duration of action, short acting such as Triazolam, intermediate acting such as Temazepam and long acting ones such as Flurazepam.

The Dr . will talk about them the next lecture .

لكلٌ ركنه الذي يؤوي إليه في الملمات،
فإذا اشتد الخطب و عَصُب الكرب واستحكمت الفتن و تكاثرت المحن لجأ كل إنسان إلى الركن الذي يحميه ويؤويه و يسعده و يرضيه فترى أن ما يخرج منه في العصيب من تلك الأوقات هو ما ركنَ إليه فيها
و تنبثق تصوراته و أفعاله و مفاهيمه للأحداث عن هذا الركن، فترى بعضهم ركنه عنصرية شمطاء أو قبلية حمقاء أو انتماءات بالية و ولاءات فانية
فإذا لجأ كلٌ إلى ركنه
فعليك بركنك الركين و حبلك المتين كتاب الله و سنة نبيه لا تُقدّم عليهما و لا تَصدُر عن غيرهما و انظر فيهما قبل حكمك على أي نازلة أو حدث
فإذا اغتر كلٌ بركنه و فاخروا بما لديهم ففاخرهم و قل :" إنما وليّيَ الله " .

إعداد : طارق ليث التل