بسم الله الرحمن الرحيم

Analgesics & Sedatives pt.2

MID | Lecture 2

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

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PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسْمِ اللَّهِ الرَّحْمَٰنِ الرَّحِيمِ

لَا الشَّمْسُ يَنبَغِي لَهَآ أَن تُدْرِكَ الْقَمَرَ وَلَا الَّيْلُ سَابِقُ النَّهَارِۚ وَكُلٌّ فِي فَلَكٍ يَسْبَحُونَ (٤٠)

{ وَكُلٌّ } من الشمس والقمر، والليل والنهار، قدره الله تقديرا لا يتعداه، وكل له سلطان ووقت، إذا وجد عدم الآخر، ولهذا قال: { لَا الشَّمْسُ يَنْبَغِي لَهَا أَنْ تُدْرِكَ الْقَمَرَ } أي: في سلطانه الذي هو الليل، فلا يمكن أن توجد الشمس في الليل، { وَلَا اللَّيْلُ سَابِقُ النَّهَارِ } فيدخل عليه قبل انقضاء سلطانه، { وَكُلٌّ } من الشمس والقمر والنجوم { فِي فَلَكٍ يَسْبَحُونَ }أي: يترددون على الدوام، فكل هذا دليل ظاهر، وبرهان باهر، على عظمة الخالق، وعظمة أوصافه، خصوصا وصف القدرة والحكمة والعلم في هذا الموضع.

بسم الله

Opioids

Weak opioids

- Codeine
- Tramadol

Strong opioids

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

- **Heroin is not a drug; it is an illicit drug.**

اللهم اجعلنا من جند الخير دلّنا عليك أرشدنا إليك علّمنا منك فهمنا عنك و وأعذنا من مضلات الفتن ما أحييتنا ..اللهم وجّهنا لما خلقتنا له واصرفنا عما نهيتنا عنه ولا تشغلنا بما تكفّلت لنا به..

Morphine

We start our journey with drugs in this semester with **morphine**.

- Morphine has ***two types of usage:***

(1) questionable usage (IN THE PAST) , it was used in **myocardial infarction (MI) with pulmonary edema**. Morphine affects the **vagus nerve**, which can cause **bradycardia and hypotension**. This effect **reduces the workload of the heart** during an MI.

(2) real clinical usage (NOWADAYS) in everyday practice , especially in **cancer patients**, where it is commonly used for pain relief (analgesia)

- Morphine is available in ***three forms***:

(1) oral

(2) injectable – which includes **IV (intravenous)** and **less commonly IM (intramuscular)**

(3) subcutaneous, which is **mostly used**. Morphine is a **lipophilic drug** this property allows **high penetration into tissues .**

- *The most important point in morphine therapy is **dosing**.* When we talk about dosing, we usually relate it to the **half-life** of the drug.
- The half-life of morphine ranges from **1-4 hours**, but its **analgesic activity continues for about 4-5 hours**. However, because there are **differences in metabolism between individuals in the population**, the half-life may vary from one patient to another. Morphine is usually **dosed 4 times per day**, because increasing the dose too much may affect the **respiratory centers in the brain** and lead to **respiratory depression**.
- Physicians must be **very careful with dosing**, especially in **cancer patients**, because cancer is a **chronic disease**, meaning the patient may take morphine **for months**. Therefore, we must **not exceed the maximum tolerated dose**, which means the **highest dose the patient can safely tolerate without serious side effects**. Treatment usually begins with a **specific starting dose**, for example **15 milligram**, given **4 times per day**.

Morphine

سبحان الله وبحمده

- With time, ***tolerance*** may develop. With long-term use, the body can become used to morphine, causing it to lose some of its effectiveness (tolerance). As a result, you may need higher doses to achieve the same level of pain relief. When tolerance appears and the analgesic response decreases, we **increase the dose gradually**, but **not by doubling it**. For example, instead of **15 mg**, the dose may become **20 mg - four times per day**. Usually the increase is **small**, such as adding about **15 mg to the total daily dose**. However, we must **not increase the dose excessively**, because of **respiratory depression**, which can be dangerous or even fatal.
- clinical scenario :

A common clinical scenario occurs in **cancer patients who are already receiving the maximum tolerated dose**, such as **15 mg or 20 mg four times per day**, which is already **close to the maximum limit**. In these patients, a **pain flare** may occur (which is a sudden, temporary, and often intense increase in pain for someone living with chronic pain), even though the patient is already taking morphine. This happens because the **intensity of the pain becomes extremely high**, and the **opioid receptors cannot fully control this sudden increase in pain**.

- In this situation, we follow a specific rule. If the patient is taking **60 mg of morphine per day**, we give **(1/6) of the total daily dose** as an additional dose to control the pain flare.
- For example, **60 mg ÷ 6 = about 10 mg**. It is **very important not to exceed this one-sixth dose**, because the patient is already near the **maximum tolerated dose**, and the **respiratory center may already be affected**. Giving more than **1/6 of the daily dose** may cause **severe respiratory depression**, which can be life-threatening.
- If morphine is given in an **injectable form**, such as **subcutaneous or intravenous injection**, the usual dose given for breakthrough pain is about **3-5 mg**. When a **pain flare occurs** in patients receiving morphine through **injection, catheter, or a morphine pump**, the same rule applies: **do not give more than (1/6) of the total daily dose !**

mg=

Oxycodone & Fentanyl

- **Oxycodone** is considered the **"brother of morphine."** It is **similar to morphine** in almost all properties we discussed, except:
  1. It is **only available orally**.
  2. It has a **longer half-life**.
  3. It is **dosed 2-3 times per day**, which leads to **less tolerance** and **less euphoria**.
- **Availability:** Not present in **Jordan**, but it is **the most commonly used opioid in the USA - high addiction-**.
- Fentanyl is **about 100 times more potent than morphine and oxycodone**. It is **more active**, works **very fast**, and its effect **finishes quickly**. Its **half-life** is much shorter than morphine, about **20-30 minutes**, its **activity in the body lasts about 45 minutes**.

  Half-life refers to the time the drug stays in the blood.

  Activity (duration of effect) refers to the time the drug actually produces pain relief.

  - Because fentanyl starts and finishes quickly, it is ideal for **titration**. Titration means **giving the drug, monitoring its effect, and adjusting the dose** – increasing if there is no effect, or decreasing if excessive. Fast-acting opioids are needed for titration because their **duration of activity is short**, allowing rapid assessment of effect.
  - **When is titration needed?**
- During **operations**, because the patient may feel pain during surgery or if the operation is prolonged. Modern general anesthesia often uses opioids to **augment the effect of anesthesia**, because anesthesia alone **does not provide sufficient analgesia**, except at very high, potentially toxic doses. By adding opioids like fentanyl, we can **reduce the anesthesia dose safely** while achieving stronger pain control.

Fentanyl

"لا إله إلّا أنت سبحانك
إنّي كنت من الظالمين"

- **Why fentanyl is preferred for intraoperative analgesia:**

1. The patient may be **hemodynamically unstable**, so a short-acting drug is safer.

2.Opioids and anesthesia both cause **nausea and vomiting**, so using a **short-acting opioid** ensures that the effect of opioids wears off by the time the patient wakes.

- Morphine lasts about 4 hours, which is **too long** for intraoperative use.
- Fentanyl is fast-acting, short-duration, and suitable for titration.
- If fentanyl is not available, morphine may be used as an alternative.
- Fentanyl is **very potent**, so it is given in **microgram doses** due to its **narrow therapeutic index**.
- sublingual forms exist in some countries, because sublingual is **controlled** (no a**bsorption, no metabolism, and no hepatic effects)** unlike oral tablets. In **Jordan**, fentanyl is available as **patches** (sustained low-dose release for 48 hours).
- **(pain flare) scenario:**

  If a patient is using **fentanyl patches** and experiences a **pain flare**, management includes:
  - Giving a **low dose of morphine**, or
  - Giving a **very low dose of fentanyl (1/6 of total daily dose)**.

- The **narrow therapeutic range** makes it critical to use **very small doses (10–30 micrograms)**
- In the USA, oral fentanyl tablets are available with less control, leading to a high risk of overdose — on average, **one American dies every seven minutes** from fentanyl misuse.

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

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.

  - ❑ Metabolism of morphine is via phase 2- we add glucuronide
  - ❑ Morphine-6-glucuronide remains pharmacologically active and acts as a μ-opioid receptor agonist, whereas morphine-3-glucuronide lacks opioid receptor activity.

- 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,

  - ❑ This clinical issue from morphine metabolites is much more likely to occur in patients with renal insufficiency.

Hydromorphone

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

Not present in Jordan, its used as a substitute to the other opioids when the patient has renal failure.

Mepiridine

- Also known as pethidine, an important drug even though its use has declined.

- it binds to μ receptors and kappa receptors- another type of opioid receptors. (There are 3 types of opioid receptors μ ,kappa and delta.) Similar to morphine it's a strong μ receptor agonist- making it a good analgesic. On the other hand, it differs from morphine in 2 things
  1) Meperidine is more active on kappa receptors compared to morphine
  2) Meperidine is less potent than morphine, with approximately one-tenth the analgesic potency. (5mg dose of morphine is compared with 25 or 50 mg dose of Meperidine). There's variation between populations though!

- It has 2 main uses:
  1) Labor; since it's the least likely opioid to reach the respiratory center of the fetus, thus least likely to cause respiratory distress to the fetus
  2) Shivering; shivering occurs in post operative patients due to multiple causes- mainly anesthesia. It occurs widely In labor as well. Its activity is dependent on the kappa receptors that are connected to thermo-centers in the brain. It lowers the shivering threshold in the hypothalamus.

- <u>High yield: "There's no drug like mepiridne for shivering"</u>

- Tramadol and dexamethasone can be used, but nothing is as good as mepiridine. We do worry about the side effects though, especially due to the vulnerability of patients in labor + post operation..
  so instead we start with:
  1) blankets
  2) tramadol or dexamethasone
  3) Last option; mepiridine
- <u>We can make a general statement and say its mostly used in the labor room- for anti-shivering + analgesia</u>

(Mepiridine, pethidine)

- Repetitive dosing leads to accumulation of the toxic metabolite normeperidine (normeperidine) (this metabolite is toxic for the CNS)

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

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

- It has a half life of 5 hours so some doctors give 4 doses of 50mg a day -it should not be used more than 3 days in this manner- or you run the risk of the mentioned CNS toxicity

- It is renally cleared, and use of meperidine in patients with kidney disease is not recommended . We avoid It in patients with renal insuffienecy, since normeperidine (the toxic metabolite) gets excreted by the kidneys

اللهم صلِّ على محمد وعلى آل
محمد كما صلّيت على إبراهيم
وعلى آل إبراهيم إنّك حميد مجيد

Mepiridine

- **Used in cases of:**
- Obstetric labor
- Shivering

Discussed in slide 12

Methadone

- The longest half life amongst all opioids, there's variations in different populations, but it falls in the range of 9-36 hours.
- Regarding dosing it's given 1 time per a day:

Morphine is dosed- 4 times
Mepridine- 3-4 times
Oxycodone- 2-3 times

- It's use comes in addiction, if a patient is addicted to the other opioids- the best treatment approach is methadone, a strong μ receptor agonist. Its benefit lays in the fact that it doesn't peak like the other drugs, thus the euphoria is limited.
- We try to reduce the euphoria form the patient + treat the physical dependence. You're switching from a sharp peak 4-5 times a day to 1 milder peak a day. A pill is given daily for the duration of 6 months.
- With time, grieving and seeking of the drug lessens. we augment this treatment with CBT (cognitive behavioral therapy)

- Its other use is when we are trying to taper a cancer patient off morphine or fentanyl. Its easier to taper with methadone- a single pill for 3 weeks is sufficient. Whilst tapering with morphine would require 2-3 months.
- This tapering is purely for physical dependence not addiction (psychological dependence)

- We can summarize its 2 uses as: 1) tapering and 2) addiction treatment

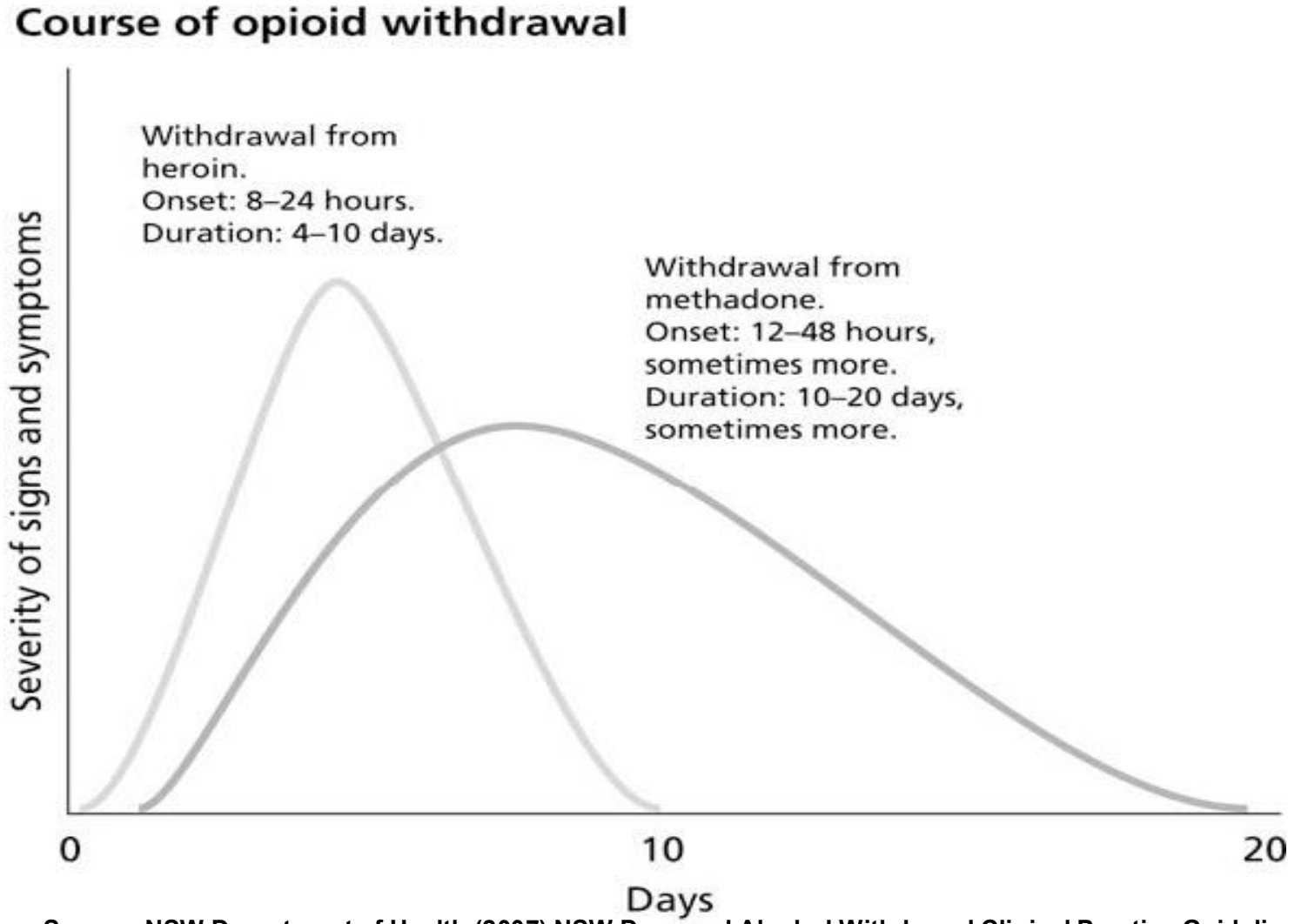
Methadone

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

  abuse. why?????

Methadone

- The onset and duration of morphine is less but it has a sharp peak- our biggest issue is with this peak.
- In methadone- technically in 20 days the withdrawal symptoms would be gone, but don't forget addiction is all about psychological dependence not physical. It's a complex issue we will revisit when we talk about nicotine and alcohol
- Sometimes methadone is even given for 1, 2 years or even life long- in the treatment of addiction.



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

Continuing on methadone- opioid rotation

- In palliative cancer treatment patients taking morphine or fentanyl develop tolerance and physical dependence (not addiction since they're not liable for that)
- They start to experience painful flairs (due to tolerance) and increasing the dosage does not help, what's the cause and what's the right protocol in this case?
- This means the patient developed hyperalgesia, in this case I start the rotation of opioids- switching him from morphine/fentanyl to methadone. The key is to put the patient on a different opioid compared to the original opioid used- and methadone has a specific characteristic. It binds to the NMDA receptor- a glutamate receptor in the brain. Antagonizing said receptor reduces pain, thought its not a very strong analgesic. Due to that, our body treats methadone and morphine as 2 separate drugs, allowing us to restore μ-receptor responsiveness to other opioids like morphine or fentanyl.
- You're not required as a general practitioner to rotate opioids, but you should know how.

- We can also rotate morphine with fentanyl but its less effective, the ability to rotate between those 2 opioids falls in the fact that morphine is a natural opioid agonist whilst fentanyl is synthetic, so even though they bind to the same receptor, our bodies treat them as 2 separate drugs-

- "Best drug for rotation is methadone due to its activity on NMDA receptors"

- Even sometimes when we are initiating therapy, if a patient is unresponsive to morphine, he may respond to methadone- since it has a different mechanism of action.
- Morphine and other opioids are ineffective against neuropathic pain, with the exception of methadone, it has some efficacy.

- A quick summary on methadone- we use it in:
  1) Tapering for physical dependence 2) addiction treatment 3) non-responding pain 4) opioid rotation

سبحان الله وبحمده عدد خلقه ورضا
نفسه وزنة عرشه ومداد كلماته

Weak opioids: Codeine and Tramadol

1) Codeine; **partial** μ-opioid receptor agonist used as an antitussive. There's no need to use a full agonist for the treatment of cough. It's also applicable for- moderate pain such as a tooth ache. These are its 2 main uses. Codeine gets metabolized in the body and gets converted to morphine via CYP2D6. 13.5% of Jordanians have more than 2 alleles for this enzyme, thus more than 2 proteins. This is a very important topic we will continue next time
2) Tramadol- will be discussed next lecture as well

Tramadol

- 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

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

الحمد لله رب العالمين

PHARMACOLOGY QUIZ LECTURE 2

رسالة من الفريق العلمي

الغاية من خلقك و وجودك هنا استحضر دائما

وَمَا خَلَقْتُ الْجِنَّ وَالْإِنسَ إِلَّا لِيَعْبُدُونِ}

{وَإِذْ قَالَ رَبُّكَ لِلْمَلَائِكَةِ إِنِّي جَاعِلٌ فِي الْأَرْضِ خَلِيفَةً }

{هُوَ أَنشَأَكُم مِّنَ الْأَرْضِ وَاسْتَعْمَرَكُمْ فِيهَا }

عبودية

استخلاف

عمارة

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

اللهم إنا نستودعك أهل غزة والسودان والإيغور والمسلمين المستضعفين في كل مكان، اللهم احفظهم بحفظك، واكلأهم برعايتك، وأمدّهم بعونك وقوتك.

اللهم كن لهم ناصرًا ومعينًا، وحافظًا وأمينًا.

اللهم الطف بهم في مصيبتهم، وارحم شهداءهم، وداوِ جرحاهم، واشفِ مرضاهم، وفكَّ أسرهم، وسدِّد رمي مجاهديهم.

اللهم اربط على قلوبهم، وثبّت أقدامهم، وانصرهم على من ظلمهم.

اللهم اجعل لهم من كل همٍّ فرجًا، ومن كل ضيقٍ مخرجًا، وارزقهم من حيث لا يحتسبون.

اللهم إنا نعوذ بك من القهر والخذلان، ونسألك أن تعجّل لهم بالنصر والفرج القريب يا قوي يا متين.

اللهم احفظ بلادنا الأردن من كل شر.

وحسبنا الله ونعم الوكيل

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