PHARMACOLOGY

◉ Sheets ○ Slides

Number: 19

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Subject: Macrolides & Aminoglycosides

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بسم الله الرحمن الرحيم

Macrolides

Some points about Macrolides were taken in the past lecture & here we continue. (Note that the arrangement of ideas in this sheet isn't exactly the same as in the record & the sheet was written based on the record of section 1)

- 3 main examples of Macrolides:

  - **Erythromycin** (Gram +ve)
  - **Clarithromycin** (Gram +ve and more Gram –ve)
  - **Azithromycin** (Gram +ve and most one to cover Gram –ve)

- Trade name for Azithromycin is "Zithromax". (The doctor kept saying Azithromax). So → **Azithromycin** = **Zithromax** = **Azithromax**.

- Azithromycin bacterial spectrum is similar to that of Penicillins', so it can be used as a substituent for it. (Incase of Penicillin-sensitive patients)

- Generally, as "K.pneumonia" is a cause for community-acquired pneumonia, It needs no hospitalization & the drug of choice was **Zithromax**
but! Misuse of Zithromax leaded to increasing the issue of resistance
so, The drug **Telithromycin** is now used instead.

- Azithromycin can be used for Acne (but not very potent for it → not drug of choice, drug of choice is **Doxycyclin**)

- Azithromycin is drug of choice for:
  - Atypical Pneumonia
  - Community-acquired pneumonia → (because its spectrum of activity includes Pneumococcus, Mycoplasma, and Legionella.)
  - Corynebacterium diphtheria & Corynebacterial sepsis
  - Respiratory, Neonatal, Ocular & Genital Chlamydial infections

P.S. You will <u>not</u> be asked about this part in the exam, it's for general knowledge.

- **Clarithromycin**: Effective against Mycobacterium avium intracellulare which can cause chronic lung disease in elderly or immunologically compromised individuals.

- **Clarithromycin**: Adjunct in treatment of duodenal ulcer (H. pylori)

- Recalling from the past lectures, it was mentioned that **Doxycyclin** could also be used as a drug of choice for "Chlamydial infections" (especially Chlamydial urithritis).
  but problem is, Doxycyclin must be taken for 7 days (100g twice/day). That's kinda inconvenient!
  solution is, 1g of Zithromax for **only one day** will be enough to treat the infection. → (Magical) ←

- In treating "Upper-Respiratory tract infections", 2 drugs of choice could be used:
  either Augmentin (for 7 days, 2-3 times daily)
  or Zithromax (for 3 days, 1g/day).

P.S.) Although both are drug of choice but let's have a look on <u>these points</u>:

- When Augmentin is more preferred, it's because it's bactericidal (Zithromax is bacteriostatic).

- Pharmacists prefer Zithromax, especially for children. (If they don't want to do a skin-test for penicillin allergy).

- Zithromax is more expensive.

- In USA, you can find 1g pills of Zithromax.
- In Jordan, 500 mg pills are prescribed, so you need to take 2 pills a day instead of taking 1.

- Why do we take Zithromax for low doses and only for short times?

  Because the drug penetrates into most tissues (except CSF –Cerebrospinal fluid-), exceeding serum concentration of the drug by 10-100 folds & the drug is slowly released, making it a drug with a high elimination **half-life of (2-4 days in tissues) ≈ 3 days.** (Sustained release of the drug)

- The only antibiotic that you need a loading dose (1 grams = 1000 mg) of it is **Zithromax**.

  Why? Because if you take 500 mg, most of the drug will go to the Adipose tissue and blood levels will be very low & the loading dose is given to buildup high blood concentrations to exceed the *MIC* (Minimum Inhibitory Concentration). **By that**, In the 1st day you will take 2 pills of 500 mg at once, 2nd & 3rd day you will take the 2 pills separated, one at day & one at night.

- Half-life of 3-4 days & the drug is used for 3 days → that means the drug will remain in the body for at least 9 days. *(usually 12 days)*

- MIC for "Chlamydia" is lower than this of "Upper-Respiratory tract infections" → So, a lower period of Zithromax intake is needed for Chlamydia.

Side effects of Macrolides:

- The macrolide with most side effects is **Erythromycin**.

- Erythromycin side effects: GI disturbances, Skin rashes, Hearing disturbances, Fever & Jaundice.

- Newer agents (**Clarithromycin** & **Azithromycin**) has one side effect in common with Erythromycin which is **GI disturbances** but not as serious.

CYP3A4 (Cytochrome P450 system):

- CYP3A4 system works on metabolizing some Narrow therapeutic index drugs (close to toxicity). → e.g. **Corticosteroids - Cyclosporine - Digoxin - Warfarin. (CCDW)**

- Inhibiting CYP3A4 will inhibit the metabolism of these drugs and they will accumulate in the blood causing **toxicity**.

- CYP34A inhibitors:
  - Erythromycin (Excellent)
  - Clarithromycin (Good)
  - Azithromycin (Bad)

- Note that **Excellent** inhibitors are the **worst** to your health!

→ So **don't** take these 3 Macrolides when you're taking any of the CCDW drugs.

Aminoglycosides

- The only bacterial protein-inhibiting antibiotics.
- Their spectrum is like "**Aztreonam**" (Monobactam)

→ (Gram -ve, Aerobic, covering Pseudomonas).

Aminoglycosides include: "VERY OLD DRUGS"

①- Gentamicin ②- Tobramycin.

③- Streptomycin ④- Amikacin (New drug)

- **Gentamicin** is most commonly used since it's the cheapest.
- **Streptomycin (oldest)** is used in treatment of Brucellosis & Tuberculosis**.**

- Remember, In treatment of Brucellosis (الحمى المالطية):

  We have to take 1 month of Doxycyclin (100 mg twice daily) PLUS 1 gram injection of **Streptomycin** in the first 7 days.

  In case we couldn't find Streptomycin, we could replace it with a high dose of **Gentamicin.**

- Brucellosis is Gram -ve, but it's going to go into the cell and live with it, so you have to treat it harsh.

* Aminoglycosides clinical uses: → Against very serious infections like:

1. Brucellosis & Tuberculosis
2. Gram -ve bacillary infection (Septicemia, Pelvic & Abdominal Sepsis
3. Hospital-acquired pneumonia (usually caused by Pseudomonas)
4. Plague (طاعون)
5. To sterilize the bowel of patients who receive immunosuppressive therapy (before surgery & in hepatic coma)
6. Bacterial endocarditis (The doctor didn't mention this but it's written in slides)

* History of "Gentamicins":

- Those drugs are Nephrotoxic & Ototoxic.

- They were used a lot in 80s and 90s but in the new century doctors become reluctant (hesitated) to prescribe it.

- Aminoglycosides are **NOT** preferable drugs. → Only used when you really need them; after you try every other option but these options do not work (due to the appearance of multi-drug resistant, Gram –ve microorganisms)

  Why is that? In order to avoid its high risk of nephrotoxicity and ototoxicity.

- The real problem is not with nephrotoxicity (its reversible), our problem is with the ototoxicity (It's irreversible & idiopathic -مجهول السبب-) → So if your patient becomes deaf, he cannot be cured.

- Aminoglycosides are **<u>bactericidal</u>.** They are the **<u>strongest</u>** drugs against the G -ve bacteria; **Why?** Because they have multiple mechanisms of action rather than one mechanism. Strong enough that made them go back to the market. Although they cause nephrotoxicity and ototoxicity, we really need them nowadays, especially after the appearance of *ESBLs* (<u>Extended spectrum β-lactamases</u>).

- There is a relatively low resistance for Aminoglycosides.

ESBLs are enzymes that are produced by bacteria. The enzymes make the bacteria resistant to many kinds of antibiotics. "**Just Read**"

- <u>For example</u>: In Pseudomonas, you will find a high resistance toward the anti-pseudomonas drugs like cefepime, ceftazidime, piperacillin, ticarcillin.

  But when you talk about Aminoglycosides you won't find as much resistant.

- Mostly against Bacillus, Septicemia, Pelvic & Abdominal Sepsis caused by Gram –ve bacteria.
  - The worst thing to deal with is Sepsis (pelvic or abdominal); it takes months to get rid of any of them.
  - Septicemia is a killer.

- When you're not sure that (piperacillin + tazobactam), or cefepime are going to work and this will lead to a problem, then in many cases you'll add **Gentamicin**.

- Recalling what we took in **Piperacillin,** "It's an Anti-pseudomonal penicillin that is frequently used in combination with Aminoglycosides **<u>or</u>** Fluoroquinolones for treating Pseudomonal infection."

  Why don't I combine Penicillins with Cephalosporins?

- It's because they have the same mechanisms of action (cell-wall inhibitors). This combination will be complete failure & toxicity will increase. (Synergism might happen but it's not common in these kinds of combinations)

➔ So whenever we want combine drugs, they must have <u>different</u> mechanisms of action in order for Synergism to happen.

- I need to combine something with Penicillins or with Cephalosporins because the Pseudomonas might gain resistance during treatment, most of the time Gentamicin is given. **But** it's better to avoid Gentamicin → So I'll give **Tobramycin**.

- **Tobramycin** is the strongest drug against Pseudomonas, stronger than Gentamicin, in Jordan we can't find Tobramycin in hospitals, instead we have Gentamicin.

- **Amikacin** is the broadest antibacterial spectrum (99.9% of Gram -ve is susceptible towards it) preferred in serious Nosocomial G -ve bacillary infection in hospitals where Tobramycin & Gentamicin developed resistance.

  (Nosocomial: A disease originating from hospitals.)

  - **How** do we know if Tobramycin & Gentamicin developed resistance?

    At the end of each year, we see all of the infections that happened in this hospital, so as to determine if this hospital contains Gram –ve bacteria that are resistant to the Aminoglycosides or not. If we had a 10% resistance for Gentamicin or Tobramycin → then the drug of choice will be Amikacin.

  - Amikacin is a great drug, Pediatrics love to use it on infants because their percentage of resistance towards this drug is very minimal.

* To sum up, when do I use the Aminoglycosides?

1) Whenever there is a resistant septicemia, bacteremia, pelvic sepsis or abdominal sepsis.
2) If there was a pseudomonal infection.

(Remember that we only use Aminoglycosides when all other drugs were not useful.)

- **Aminoglycosides** are not absorbed from the GI tract, so we give them as injections.
- Administered Intramuscularly **(IM)** or Intravenously **(IV)**.

- There are serious **"Dose-Related"** side-effects occur with the Aminoglycosides. The main hazard is **Nephrotoxicity** (Pharmacological side-effect)**.**
- **Ototoxicity** is **"NOT Dose-Related"** (Non-pharmacological, bizarre side-effect of Type B)**.**

* Some main rules concerning Aminoglycosides

- ✓ Treatment shouldn't exceed **one week.**
- ✓ What if it exceeded? The nephrotoxicity will increase as it's dose-related and **Accumulation** will happen.
- ✓ To find out and monitor if there is **Accumulation** in your patient, You must find out the concentration of Aminoglycosides in his/her body.

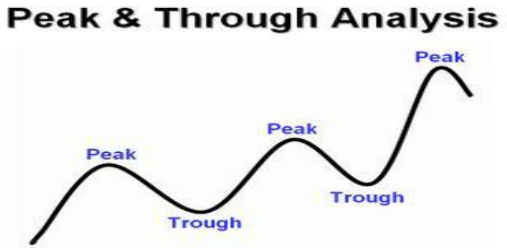
How do you monitor the level of Aminoglycosides in the blood of your patient?

Two things to do:

- Either determine the highest concentration of drug in the bloodstream **(Peak)**
- Or determine the lowest concentration before the next dose **(Trough)**

The most accurate way to measure if there is accumulation of Gentamicin or Aminoglycosides in general or not is by measuring the **Trough**.

→ So you take a blood sample from your patient and send it to the lab, they measure the trough, and by referring to specific numbers, you see if the trough exceeds these numbers, you have to reduce the dose.



~ كنّ مع الله و لا تُبالي ~

و لقد بلغتُ من التفاؤل أوجهٌ
و قلائلٌ من يفعلون قلائلُ
حتى تفاعيلُ البحور قرأتها
متفائلٌ متفائلٌ متفائلُ :)

The End ♥