بسم الله الرحمن الرحيم

Chemotherapy 8

Doctor: Manar Zraikat.

Done By: Abdullah Hamdan.

Doctor 2019

Erythromycins (Macrolides)

- Erythromycin is among a group of antibiotics which is called Macrolides.
- Macrolides generally have the same spectrum of activity like penicillin, so we can consider erythromycin among the good alternatives in some cases where patients have a penicillin allergy or β-lactam antibiotics allergy in general.
- One of the main advantages linked to Erythromycin is being widely distributed in the body (High Volume of Distribution), It can reach some infection sites which is hard to reach sometimes, even it can reach the prostate gland for example.
- These features makes it a good option & alternative, especially for the patients who have hypersensitivity against penicillin, The Macrolides will be a good option, specifically Erythromycins.

Erythromycins (Macrolides)

- **Erythromycin is safe drug for children:**

- It can be given orally.

- Can cause nausea, vomiting, and diarrhea (Common side effect for most of antibiotics). In general, these side effects will be decreasing as long as the patient is taking his medication (تقل مع أخذ المريض الدواء).
  There is no antibiotic without side effects.

- Rarely can cause jaundice. However, speaking generally it is a safe drug.

Erythromycins (Macrolides)

- Other examples of Macrolides:

1. Clarithromycin.
2. Azithromycin.

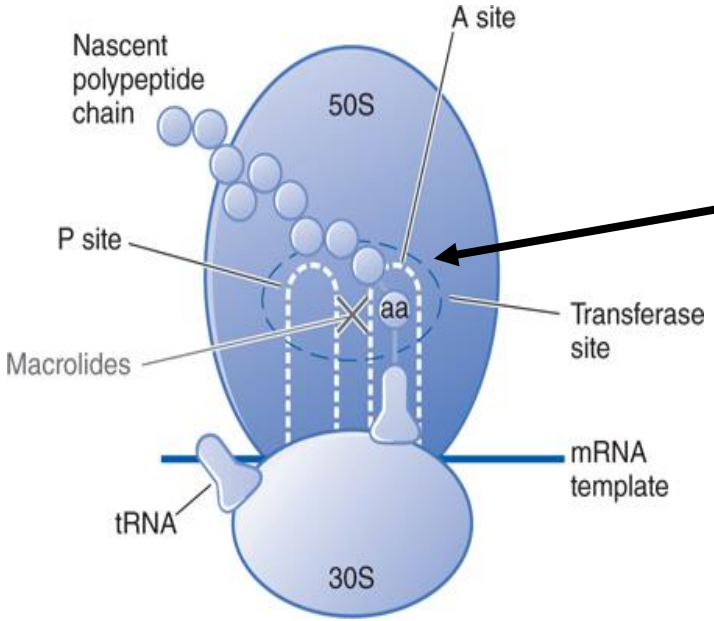
They have common features:

- Long acting, short courses (e.g. Azithromycin is prescribed as one pill for a day, and the course extend only to 3 days).

- Used to eradicate **Helicobacter pylori** (The bacteria, which is found to increase the acidity of the stomach).

- Clarithromycin & Azithromycin are 2 members of triple therapy that is used to eradicate the Helicobacter pylori, the 3rd member of this therapy is proton pump inhibitor.

The mechanism of action of Macrolides



They make a <u>reversible</u> binding to the 50S subunit, so they prevent the completion of the translation process (mRNA to a polypeptide chain).
It is reversible, so when the drug unbinds to this subunit, the protein synthesis process will take place again normally.

Inhibition of bacterial protein synthesis by the macrolide antibiotics erythromycin, clarithromycin, and azithromycin. Macrolide antibiotics are <u>bacteriostatic</u> agents that inhibit protein synthesis by binding <u>reversibly</u> to the 50S ribosomal subunits of sensitive organisms.

Lincomycin and Clindamycin

- Effective against Gram positive bacteria, like penicillins.
- Clindamycin binds exclusively to the 50S subunit of bacterial ribosomes and suppresses protein synthesis.
- Clindamycin is being misused by doctors, because it is reserved for severe cases but in fact it is being misused by doctors who are prescribing this antibiotics in simple cases where we can simply prescribe instead a weaker antibiotics.
- So misused by doctors in the treatment of simple sore throat or URTI (Could be treated with weaker antibiotics rather than using this relatively strong antibiotic.)

Lincomycin and Clindamycin

- Should be reserved (kept) for deep seated infections (more serious ones) like bone infection.
- Overuse of lincomycin (Higher doses or longer courses) caused many cases of **Pseudomembraneous colitis** caused by overgrowth of resistant intestinal flora **(Clostridium difficile).**

Vancomycin

- Is one of the strongest antibiotics.
- Very toxic agent (لا يستخدم إلا إذا الحالة استدعت هذا الأمر) : ototoxic and nephrotoxic.
- Vancomycin is reserved only for hospital use (close medical monitoring) for severe cases (Staphylococcus, Sever Infections) in cases where other antibiotics have not worked.
- Reserved for severe Staphylococcal infection, given by slow IV infusion.
- Given orally for Pseudomembraneous colitis (Which is caused by medical errors of prescribing a strong antibiotics such as Lincomycin, for higher dose intervals or higher doses. Also, There are some infection cases that doesn't require from doctors to give patients strong antibiotics)

Vancomycin

The mechanism of action:

- Vancomycin inhibits the synthesis of the cell wall in sensitive bacteria specifically by binding with high affinity to the D-alanyl-D-alanine terminus of cell wall, which is a part of the peptidoglycan structure, which forms the rigid part of the cell wall for the bacteria. It will inhibit the structure of peptidoglycan therefore it inhibit the synthesis of the cell wall.

- Hence, this drug is bactericidal for dividing microorganisms, because cell wall is very essential for bacteria to continue it's vital activities .

- D-alanyl-D-alanine: A dipeptide comprising D-alanine with a D-alanyl residue attached to the α-nitrogen. It is a component of bacterial peptidoglycan and forms an important target for development of antibacterial drugs .

Tuberculosis

- The most important communicable disease in the world.
- Caused by Mycobacterium tuberculosis.
- Treating TB is a major therapeutic challenge.
- The problems associated with treating tuberculosis that it treated with high courses intervals (it will take a long time) and it need more than one agent of antibiotic for treatment. Why?

Because the ability of the tubercle bacillus to remain for a long time dormant (no activity) but viable and capable of causing disease in any moment.

Groups at high risk for tuberculosis infection

1. **HIV-infected persons.**
   On the top of the list.

2. **Immigrants from countries with high rates of TB.**

3. **Persons taking immunosuppressive agents.**
   Those who need to make organ transplantation so they need to suppress the immune system for a while, therefore they are more susceptible to be infected.

4. **The homeless.**
   The medical care is low, poor hygienic environment, nutrition state is low.

5. **Health care professionals.**

6. **Intravenous drug users.**

The three basic concepts in Tuberculosis Treatment.

- (1) Regimens must contain multiple agents or drugs for treatment. Why?
  - In the treatment for TB, resistance might occur because the course extend for a long time. So, we take multiple drugs to make resistance a non possible thing.
  - The 2nd benefit from taking multiple drugs for tuberculosis that it will make patients need a lower doses from each drug for treatment, therefore less side effects.

- (2) Drugs must be taken regularly. TB treatment course can extend from 6 months to 2 years.

- (3) Drug therapy must continue for a sufficient time.

First-line drugs

- These drugs which we use most of time (بأغلب الحالات تستخدم هذه الأدوية) , there are a second-line drugs we classify them as second line because of their high side effect.

- Treatment of TB begin with the first-line drugs.

- First-line drugs:

✓ **Pyrazinamide**
✓ **Rifampin**
✓ **Ethambutol**
✓ **Streptomycin**
✓ **Isoniazid**

To make things easy: each letter in red represents one of the first line drug.

PRESIDENT

Antituberculous Drugs
Isoniazid (INH)

- Isoniazid drug is targeting the mycobacterial cell wall.

- Primary action of isoniazid is to inhibit the completion of biosynthesis certain parts of the cell wall and inhibit the biosynthesis of mycolic acids-long, branched lipids that are attached to polysaccharide, to form part of the mycobacterial cell wall.

Antituberculous Drugs
Isoniazid (INH)

- A member of first line drugs (The first drug which is used for treatment of TB, in addition to other agents for sure).
- Rapidly absorbed after oral route administration.
- Widely distributed and excreted by the kidneys (Taking in consideration the appropriate dose for the patient and make sure that they don't have a kidney failure. However, we should do a regular and routine Kidney & Liver tests for those patients who are taking a long TB treatment course)
- High diffusion (High volume of Distribution) so it can diffuse widely in the body, and it can enter the infected cells easily.

Antituberculous Drugs
Isoniazid (INH)

- Metabolized in the liver:

• Fast metabolizers. (Metabolism faster, not high toxicity, but weaker efficacy, because the body can rid of the drug faster.)

• Slow metabolizers. (The drug life within the patient body can last longer, metabolism will be slow, so toxicity will increase)

Hence, we need carefully as doctors to chose the correct doses for each drug.

Antituberculous Drugs
Isoniazid (INH)

Toxicity: Causes neuropathy, especially in slow metabolizers. Neuropathy can be reversed easily if the patient take a Vitamin B6 course. So, they prefer to prescribe the Isoniazid with a Vitamin B6 to avoid neurotoxicity.

- If a drug is metabolized too quickly, it may decrease the drug's efficacy while if the drug is metabolized too slow, toxicity may result.

- Drugs that are metabolized by CYP2D6, certain Individuals will eliminate these drugs quickly (ultrarapid metabolizers) while others slow.

Antituberculous Drugs
Rifampin

- Another first line drug.
- Broad spectrum activity antibiotic, so misused by doctors.
- Use in Jordan is restricted for TB and prophylaxis of meningitis contacts especially in surgery.
- It has side effects and can cause red discoloration of secretions: tears, urine etc. (يتحولوا للون الأحمر) It's not permanent, it is reversible and it will return back easily after being washed out from the body.

Antituberculous Drugs
Rifampin

The mechanism of action:

- Inhibits RNA polymerase of mycobacteria and other microorganisms by forming a stable drug—enzyme complex (bind to this enzyme in a complex), leading to suppression of the function of RNA polymerase (which inhibits the initiation of chain formation in RNA synthesis)

- Inhibition of RNA polymerase or synthesis, it will inhibit the whole process of DNA replication, Protein transcription and synthesis, the growth of the cell. So, all of them would be stopped.

- RNA polymerase also known as DNA-dependent RNA polymerase: is an enzyme that produces primary transcript RNA.

Antituberculous Drugs
Streptomycin

- An aminoglycoside, 1947.
- Was the first effective antituberculous drug. It should be given with other drugs.
- Should be given by injection, resulted in noncompliance of the patients.
- It can’t be used only, we need to give it with the first-line agents.

Antituberculous Drugs
Streptomycin

- Is used in treatment with a lot of cases, and it is linked to Ototoxicity.
- Resistance developed very rapidly which makes it less favorably to use.
- Replaced by isoniazid.
- Still used in some cases.

إذا كنت تريد معرفة قدر الله في قلبك
فانظر إلى من تلجأ عند نزول البلاء
بك، فإن الإنسان لا يلجأ إلا إلى أعظم
نصير في قلبه.

— عبد العزيز الطريفي