



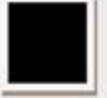
Medical Committee
The University of Jordan



PHARMACOLOGY

Lecture No.: 30

SHEET



Doctor Name: Malik Zuhlif

Written By: Ruba Al-Ghalayini

SLIDES



DONE BY: ISSA KHASHAN

TETRACYCLINES AND MACROLIDES

-Tetracyclines are protein synthesis inhibitors, bacteriostatic antibiotics
-They have a broad spectrum, it includes gram positive and negative bacteria, some spirochaetes, anaerobs and some protozoa (ex: amoebae)

- **BUT** the problem they are facing is the resistant bacteria so most of the activity is lost. All tetracyclines (doxycyclin, Methacycline, Moxycycline, minocycline), except Tigecyclin, are not active anymore against most staph, strep, H-influenza that cause upper respiratory tract infection.
- **And the reason behind this activity loss is that** there is a plasmid within the bacteria that encodes for an energy-dependant efflux pump on the cell wall of both the gram+ve and -ve bacteria. So whenever tetracycline gets in the bacteria, it will be pumped out of the bacterial cell, thus lowering its activity.
- Though most tetracyclines now don't have an activity against gram+ve, -ve bacteria and anaerobs but they are still very effective against six types which are: **Chlamydia, Mycoplasma, Cholera, Brucella, Borrelia, Rickettsia.**

1) Chlamydia: causes Chlamydia urethritis, Chlamydia conjunctivitis. It's not common here in Jordan since it's a STD, but it's more common in USA where they have one million cases each year. The drug of choice until now is **Doxycyclin** (or Azithromycin, one of the Macrolides we'll talk about, but it's more expensive, so Doxycyclin is used more).

2) Mycoplasma: Tetracyclines are effective against mycoplasma pneumonia since it does not even have a cell wall so there is no pump. Whenever we suspect that it's a community acquired pneumonia atypical mycoplasma we use doxycyclin, but a lot of doctors don't use

it as a drug of choice and they use Azithromycin instead (**Azithromycin is the drug of choice for Community acquired pneumonia**).

So can we use tetracyclines (doxycyclin, monocyclin...) in the empirical treatment of CAP?

The answer is No, because CAP could be caused by gram+ve (strep, staph) and gram -ve (H. influenza) bacteria, Chlamydia, Mycoplasma, and legionella (and sometimes Klebsiella).

-So to prescribe an empirical treatment for CAP we should cover all these 6 types, but doxycyclin is not active against gram +ve and -ve (not complete inactivity, let's say 25% of strep. is resistant to tetracyclines).

-But we use tetracyclines as a definitive treatment; when we know that the cause of this community acquired pneumonia is Mycoplasma for example.

* Remember that mycoplasma lives in military camps, schools, universities and kindergartens (wherever there are crowds of people in a certain place).

3) Lyme disease: it's caused by spirochetes (a spiral bacteria called Borrelia), it's a North American disease, not common in Jordan.

4) Cholera: we don't worry about it anymore, but if there was an outbreak of cholera, doxycycline would be a good choice.

5) Brucella: it is still susceptible for tetracyclines, **doxyxycline** is the drug of choice.

Treatment of Brucellosis:

We usually use tetracyclines for 7-10 days, but in case of Brucellosis it's different. Brucella lives within the cells so we have to treat it longer by

giving 100 mg doxacycline twice daily for **45 days**, plus giving an injection of Streptomycin (one of the aminoglycosides) everyday for a week.

6) Rickettsia (rocky mountain fever): it's in USA we don't have any in Jordan, but there was a case last year in Mafraq, they suspected it was Rickettsia but the doctor does not think we have any.

- **Clinical uses of tetracyclines:**

- 1) Mycoplasma and Chlamydia infections.
- 2) For Brucellosis usually in combination with aminoglycosides.
- 3) They are used in combination regimens to treat gastric and duodenal ulcer disease caused by Helicobacter p.
- 4) Acne (doxacycline).
- 5) syphilis.

-Those uses are for all the tetracyclines except **Tigecyclin**.

- **Tigecycline:** it's different. The usual structure of tetracyclines is changed which makes the molecule NOT a substrate for the efflux pump, but this only happens in the case of plasmid encoded pump, but when it's encoded in the chromosome itself (a **chromosomal pump**) the bacteria would still be resistant to Tigecycline and it won't be effective, such as in **Pseudomonas auroginosa** (and proteus) which are resistant to Tigecycline.

Tigecycline Spectrum: broad spectrum, everything except p.auroginosa and proteus.

Its uses: not very serious infections, we use it in intra abdominal infection and skin infection because it's active against strep and staph, and anaerobes. It can also be used in pneumonia (off-label use).

How it is given: intravenous slow infusion for 30-40 minutes

Contraindications: children and pregnant women

-Tigecycline is a quite good drug but there is a problem that has been reported which lead the FDA (Food and Drug Administration) to add a black box on the leaflet of tigacycline.

This has resulted from long clinical trials and what is called meta – analysis; they found that the mortality rate (death rate) is higher if Tigecycline is used, in comparison with imepenem (Tienam) and piperillin. 4% died of those taking Tigercycline, while only 3% died from those taking other drugs. (one of the trials: 2460 of the patients take Tigecycline, 66 died. While other 2400 patients taking other antibiotics and only 46 died).

- What's important to know is that (Tigecycline should be reserved for use in situations when alternative treatments are not suitable).

So if this drug increases the mortality rate, why do we need to use it?

Because sometimes we don't really have another option, when the patient is not responding to any of the antibiotics we're giving, then we have to use it. And this leads us again to the (risk: benefit) ratio; if the benefit outweighs the risk, we use it.

So that's why tigacycline is approved for the use now in 2014-2015 although it has been labeled in a black box in 2012. That's called post

market surveillance (monitoring the safety of the drug after it has been released on the market). In America they do it differently, the doctor has to report every case (for example he writes: my patient has been treated with a specific antibiotic and he responded that way), we don't have this here but hopefully we'll reach this someday.

Notes on tetracyclines:

- The Tetracyclines are usually administered orally but can be given parenterally..
- Absorption from the gut is irregular and better in the absence of food.
- **Since Tetracyclines chelate di- and trivalent metal ions, forming insoluble complexes, absorption is decreased in the presence of milk, certain antacids and iron preparations:**

This means that tetracyclins bind dications (Calcium, Magnesium) and trications (Aluminium), Aluminium and Calcium are found in antacid, Calcium is found in milk, and iron is charged too (Fe^{+2} , Fe^{+3}), and when tetracycline binds to these metal ions they form an insoluble complex and this decreases its absorption. That's why you shouldn't take milk or antacids with tetracyclines.

Side effects:

1) They are deposited in growing bones and teeth, causing staining and sometimes dental hypoplasia and bone deformities.

So Tetracyclines should never be given to children nor to pregnant women or even nursing mothers. It precipitates in the growing bones and teeth of children causing deformities, and it also causes hepatotoxicity in pregnant women, so you should NEVER give tetracycline for a pregnant woman.

2) **Phototoxicity** : the sensitivity to light; it means that the patient would get severe sun burns when he is exposed to the sun. Here in Jordan the sun is not that burning, but in Saudi Arabia for example, or Australia where the sun is not extremely burning but rather very close to the land (**Melbourne** in Australia is the place where the sun is the closest to the land), so if you're taking tetracycline and went there to the sea tanning you would be sun-burned.

The (Doxycycline and Monocycline) slide is Read only.

And that was the end of tetracyclines, but what's next the doctor usually explains it for dentistry students so it's just for our own information:

-Sometimes we make an advantage of a disadvantage, for instance, there is a drug called Nexidin that was used for treating hypertension, the patients using it have observed an increase in hair growth, so companies have used this drug to make another one called (rogaine) for bald people. The same happened here, it's true that tetracycline deposits in bones in children causing bone deformities or hypoplasia, but in adults it will deposit within the area under the teeth, treating what's called periodontitis, (an inflammatory disease affecting the tissues that surround and support the teeth).

-Acute Necrotizing Ulcerative Gingivitis appears with stress.

College students can get it during finals and people breaking up can get it. So you just calm down take it easy people!

Macrolides

Three drugs: Erythromycin (very old, very cheap), Clarithromycin , Azithromycin, and a new drug called **Telitromycin** we'll talk about next lecture.

Those three drugs are very common and used everyday (community drugs). Macrolides are bacteriostatic.

The spectrum:

1.Chlamydia. 2. Mycoplasma. 3) Streptococcus. 4) Staphylococcus. 5)Legionella. 6) H. influenza.

And those six bacteria are the causes of community acquired pneumonia, so the drug of choice for the empirical treatment of community acquired pneumonia is **Azithromycin**.

If a pregnant woman has Chlamydia, she should not be given doxycyclin (tetracycline) so she is treated with one of the macrolides (Azithromycin for example).

All antibiotics should be taken for at least 5-7 days to keep the pressure on the microorganism to fight resistance, but in case of Azithromycin (in the upper respiratory tract infection) it is taken for 3 days only; 2 tablets at the first day, and another 2 on the second and third day(at morning and evening), while Augmentin for upper respiratory tract infections should be taken for seven days. That's why in America Azithromycin is only of 3 tablets, 1 gram each.

And when using doxycycline for the treatment of Chlamydia, we give 100 mg for a week (twice daily), while if we're using Azithromycin we give only 1 gram for 3 days.

Azithromycin:

Azithromycin penetrates into most tissues (except cerebrospinal fluid, so it does not have an activity against meningitis), with tissue concentrations exceeding serum concentrations by 10- to 100-fold.

- The drug is **slowly** released from tissues (tissue half-life of 2–4 days) to produce an elimination half-life approaching 3 days.

This means that when you take the drug it will go to the tissues and stay there, as a reservoir to sustain release of the drug, so the patient takes Azithromycin for only 3 three days and it will keep working for 9 days.

And 1 gm of Azithromycin for Chlamydia is enough because it will stay for 5 days in the body, so it would be enough to take it just once.

Next lecture we'll continue talking about macrolides inshAllah.

Life begins at the end of your comfort zone.