Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 31

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SHEET ■

SLIDES □

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"بسم الله الرحمن الرحيم"

MACROLIDES & AMINO GLYCOSIDES

❖ Macrolides:

In the last lecture we ended up talking about Azithromycin, and now a colleague of us is going to talk about a new drug **"Telitromycin":**

- Telitromycin is a macrolide and like all the other macrolides it is a protein synthesis inhibitor , bacteriostatic that binds to the **50s subunit** of the bacterial ribosome, so inhibits the growth of the polypeptide chain. It's taken orally once a day for 7-10 days, rapidly absorbed and its **half-life** is 10 hours.

- 1/3 of it is excreted unchanged in the bile and the urine

- The (biliary) route is usually favored, and mainly metabolized in the liver

- Designed to overcome resistance mechanism against **erythromycin A** within gram positive cocci

- used in the treatment of moderate community acquired pneumonia
- most common side effects : diarrhea, nausea, vomiting and dominate pain

- What is bad about it is that it may cause hepatic toxicity, clostridium difficile pseudomembranous colitis, blurred vision.

- **Warning** issued by **FDA** that this drug may cause death due to respiratory failure to *myasthenia gravis patients*, and it shouldn't be administrated by patients with low potassium and magnesium levels,why?(the Dr wanted the answer from the student the next lecture)

Now the Dr is talking:

-2004 telitromycin was approved as a good drug for **upper respiratory tract infection** and it has 4 applications : acute sinusitis, acute tonsillitis, strep.p pharyngitis (we were using penicillin G for this), and community acquired pneumonia
But because it causes **hepato-toxicity**, FDA has withdrawn most of the applications of the drug.
But why don't we withdraw the whole drug from markets?! We do a risk-benefit balance so you should ask yourself why should I risk my patient getting hepato toxicity while treating weak community infection(sinusitis, pharyngitis) that is

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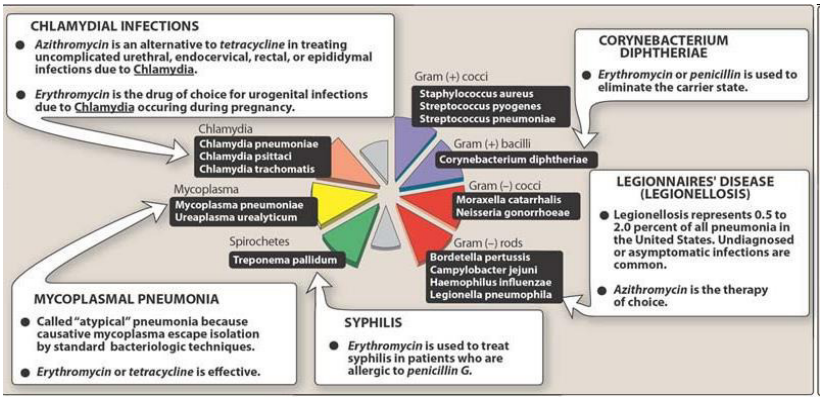
easily treated or resolved without a drug , for this reason since 2007 FDA has withdrawn most applications of this drug **except treating community acquired pneumonia** and as you know that most macrolides (Clarithromycin, azithromycin and telitromycin) are drugs of choice in community acquired pneumonia .
Remember we don't want to risk our patient with hepato toxicity so the up-to-date drug of choice in community acquired pneumonia is **azithromycin,** why? Because it cover gram positive (strep, staph), gram negative (h.influenza) and "atypical type" (mycoplasma) and legionella.

- When should we use erythromycin? We use it when there is resistance towards azithromycin.

- Now there is a resistance growing, similar to tetracycline story, there is a **pump** coming from a plasmid *pumping out* some of the macrolides and one of them is azithromycin and it's becoming common; because of this FDA was forced to keep the drug on (telitromycin). Otherwise, if it's another drug that causes hepato toxicity we will not keep it in markets, why? The approval of telitromycin faced a lot of corruption (not using true research results) that's because telitomycin was causing hepatotoxicity and there were lots of stories about it, so it wasn't considered a "clean drug".
Here is what a guy from FDA said at the time of telitromycin approval:
- "how one justify balancing the risk of fatal liver failure against one day less of ear pain"

- It's not sensible to use this drug and risk the patient with hepatotoxocity in the previous situation (ear pain=otitis media) or sinusitis or tonsillitis (after some time of usage, this drug has been withdrawn from the market), so it was left to be used in cases of **community acquired pneumonia**; because azithromycin resistance is becoming a bit popular and we do this to make our patients safe as well as giving them a second choice in case azithromycin doesn't work with them or if we know that our community is having a problem of pumping out of macrolides as in tetracycline so we use telitromycin.

Now let's return back to macrolides in general:



- Erythromycin is the oldest member in macrolides that is only active against gram positive bacteria and spirochetes.

- Modern types (found in clinics these days): clarithromycin, azithromycin and the restricted telitromycin.

- They bind to the 50s ribosomal subunit and inhibit protein synthesis.

- Azithromycin(**bacteriostatic**) active against gram negative including H.influenza (causes RTI) plus mycoplasma and legionella and gram positive (strep, staph); so it's the drug of choice in **mild to moderate** community acquired pneumonia since it's bacteriostatic.

- **Severe** type of community acquired pneumonia is treated with **bactericidal** drugs (**respiratory quinolones** we will talk about them next time inshallah).

  (this is the first time we talk about Community Acquired Pneumonia **empirically** where **Macrolides** are used (mostly azithromycin), while in definitive therapy we said that we use doxycycline for mycoplasmic pneumonia but in life threatening cases we use respirator quinolone (levofloxacin)

- Macrolides are active against chlamydia, so if my patient is pregnant or nursing mother or a child, I can't give her tetracycline and the drug of choice for these patients is a macrolide whatever it is it works(in Jordan erythromycin is rare, and azithromycin in the most common). In other words we use tetracycline (*doxycycline*) to treat **chlamydia** because it' cheap but in the pregnant or nursing mother (breast-feeding mum) patients we use macrolides instead of tetracycline.

- Also macrolides "erythromycin" (not severe cases) are active against **diphtheria** and penicillin (penicillin G injected in severe cases) is active on it also. Luckily we've developed a vaccine for diphtheria so it's very common these days.

- There is a bad microorganism called **mycobacterium avium cellulare**, although it's rare but it's important for medical students because it is common in immunocompromised elderly that you will deal with a lot of them especially that they use anticancer drugs or on immunosuppressant. This opportunistic microorganism cause chronic lung disease or called inflammation.(the drug of choice is **clarithromycin**.

- Clarithromycin : Adjunct in treatment of duodenal ulcer, we give it (amoxicillin with clarithromycin plus PPI:lansoprazol). Next semester in the GI system you learn how to treat peptic and duodenal ulcers….

- Azithromycin shows particularly good activity against chlamydial urethritis. Except for its cost, it is now the preferred therapy for urethritis.

- The macrolides are administered **orally**, although they can be given parenterally if the patient is hospitalized in moderate pneumonia.

- A 1.5 years old child with pneumonia should be given cefuroxime orally or Augmentin to treat lower respiratory tract infection (pneumonia),but she refuses to take any drug orally so they had to give her an injection. They should give her Zinnat injection but there was no Zinnat so they gave her ceftriaxone injection (3rd generation of cephalosporin) which is considered acceptable in that case, instead of giving her tienam or anything with a very wide spectrum. This is the treatment because she doesn't have an "atypical" pneumonia which is caused by legionella and mycoplasma; keep in mind that community acquired pneumonia is very common especially in children.

- Azithromycin differs from erythromycin and clarithromycin mainly in *pharmacokinetic properties*, we treat chlamydia with only 1 gram of azithromycin in a single shoot, compare it with 5-7 days of 100ml gram tetracycline but we use tetracycline because it is cheaper.

- If you go to the pharmacy with a pain in your throat they will give you **azithromycin** which is expensive when you compare it with Augmentin, azithromycin comes with 3 grams in the packet only 1 gram per day [taken over 3 days only]. While Augmentin is taken over 7-10 days in cases of sinusitis or otitis media. The reason behind this short period of administration of Azithromycin is its magical pharmacokinetics.

- **Telitromycin** is a great drug but the problem is that when it is distributed in the body It goes to **macrophages** and concentrate in it, macrophages move to the sight of inflammation so it looks like you are building the drug in the inflamed area which may attack the liver causing liver toxicity.

- **azithromycin** penetrates into most tissues (except cerebrospinal fluid= NO meningeal effect), with tissue concentrations exceeding serum concentrations by 10- to 100-fold. Which means that drug moves towards tissues and stays there forming a *reservoir* so there will be sustained release of the drug.
  - The drug is slowly released from tissues (**tissue half-life of 2–4 days**) to produce an elimination half-life approaching 3 days. In other words the drug concentration graph has PEAK, little trough, PEAK, very little trough

    What explains the graph and the long half-life is that the drug is still released slowly by the kidney (because it's kept on the tissue) to achieve equilibrium between tissue and blood. In the first three days there will be a **buildup** of the

drug in tissues which needs a long time to be released into blood (**10 days**) that's why we give for 3 days only.

- In **Chlamydia** we don't need the long activity of azithromycin, we need it to be active for **5 days** only that's why we give only 1 gram of it for a single time that will stay active(above MIC) for 5 days.
- Q: which of the following antibiotics is only given for three days and approved to be effective? A: Azithromycin.
- Azithromycin is a good drug because it penetrates tissues and the available drug in the body is low; so the effect on flora is low as well the incidence of GIT problems is.
- Azithromycin relatively doesn't cause diarrhea (non diarrhetic), while erythromycin and clarithromycin do.

- Macrolides adverse effects:

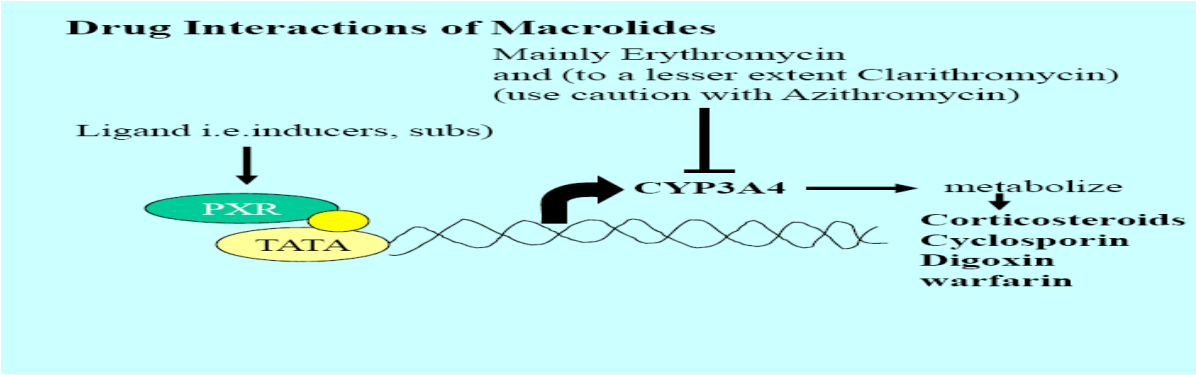
- • Ototoxicity: Transient deafness has been associated with erythromycin, especially at high dosages.

- • Cholestatic jaundice especially with the estolate form of erythromycin

- **Interaction of macrolides**

- •The problem in macrolides generally is their **bad interaction**, this interaction inhibits **CYP3A4** enzyme and because of that the metabolism of other drugs is going to be less, elevation in drugs levels occurs. This is bad especially for narrow therapeutic index drugs.

- • Mainly **erythromycin** and to a lesser extent **clarithromycin** (**major effect** on CYP3A4) , use caution with **azithromycin** (it **has the potential** to inhibit CYP3A4) .



• You should never use erythromycin with a patient who is taking *digoxin* or *warfarin*.

•What's new about macrolides?

-Effective in Community Acquired Pneumonia **empirical** treatment as well as in mycobacterium avium cellulare treatment.

-Special dose: 1 gram for Chlamydia and 3 gram for other RTI.

-They have drug-drug interaction with CYP3A4.(Major with erythromycin and minor with azithromycin)

-note: we have erythromycin in Jordan but we don't use it, it is still used in poor countries because it is cheap.

❖ AMINO GLYCOSIDES (only bactericidal protein synthesis inhibitor):

•Used in hospitals because there we are dealing with **hospital** acquired diseases or severe cases that need to be hospitalized; therefore we can't use bacteriostatic drugs we use **bactericidal** drugs.

•They are **nephrotoxic** and **ototoxic** drugs, so they shouldn't be given for more than a **week**.
Example:
A patient in the hospital with G-ve septicemia, has been prescribed with Gentamycin (one of the aminoglycosides) his doctor forgot to right a limited duration for administration of the drug and went on vacation leaving the patient with the nurse who continued giving the drug to him for 2 weeks, then the doctor came back to find his patient suffering from kidney failure.

•They should be monitored for trough and peak because they have a naïve distribution which means its distribution differs from a patient to another, so we should keep an eye on its concentration in the blood.

•When it's prescribed it should be written in a good order form(e.g: this drug should be given for five days **only,**4 times a day and monitor it for trough or peak).

•Although amino glycosides are bad drugs but we still need them why?!!

An example may explain this: - amino glycosides were very popular in 60s and 70s even in 80s (old drugs); because they have a very good activity on **gram negative** bacteria. At the same time they aren't active against neither gram positive nor anaerobic bacteria. They are opposite to Vancomycin (G+ve only) however similar to azetreonam (monobactam; G-ve only) but the difference is that the resistance is not a major issue for aminoglycosides; due to the **multiple mechanisms** of actions they have.

Q: Why are aminoglycosides bactericidal although they're protein synthesis inhibitor?

Answer**: Amino glycosides besides inhibiting protein synthesis they disturb the cell wall (dual effect), they are the fastest to kill microorganisms.** It has 2 effects together, it's like it had synergized itself.

-we use them now against the resistant problem which is getting more popular. (All **enterobacteriaceae** "enterobacter, klebsiella, E.coli" nowadays are producing extended spectrum B-lactamase **ESBL** so we get back to old drugs)

- The doctor is now talking about a paper that was made in 2009 with a head line: Do we really need aminoglycosides?
  - This question is really reasonable, since aminoglycosides are bad due to their common ototoxicity and nephrotoxicity.

•There are two important issues that discourage physician from using aminoglycosides more than they do in current clinical practice, the advanced pattern of antimicrobial resistance of today's clinical isolate in many parts of the world and the toxicity of this class of antibiotics. This is reflected in the drop of the recorded use of aminoglycosides in the recent years, that's what emerged as an important question for clinicians is whether these problems are indeed serious enough to make the choice of aminoglycosides an attractive one in most instances (not sure of the words).

-The sentry antimicrobial surveillance program shows that aminoglycosides still retain good activity against most gram negative fermenting bacilli such as E.coli, klebsiella pneumonia and enterobacter. Susceptibility rates of these bacteria towards aminoglycosides (amikacin, gentamicin and tobramycin), the susceptibility rate of these bacteria to amikacin is 97.3%, gentamycin 90%, tobramycin 89.8%.

-Some aminoglycosides show considerable in vitro activity against all three gram negatives pathogens that are ranked among the top bacterial threats (mainly

acenetobacter "common in Jordan", pseudonomas aeurognosa and the ESBL producing enterobacteretia).

- The answer of the question (do we really need aminoglycosides?) is YES indeed we need it.
-So we use them against G-ve bacteria that are developing resistance against penicillin and cephalosporin by producing ESBL like enterobactereccae (klebsiella, E.coli, salmonella, shigella, proteus, serratia,) only imipenems and meropenems are still active against them. However imipenems and meropenems still have a problem in klebsiella-pneumonia-producing-carbapinemase. Luckily aminoglycosides are active on them especially amikacin which 97.8% of the isolates are still sensitive to it (which is a high number and could be found in imipenem and meropenem in all cases other than Klebsiella where it drops to 85%), so we still need aminoglycosides in hospitals because they still retain their activity and the isolates that are resistant to other drugs are still sensitive to them, they're used to treat sepsis (pelvic sepsis), bactericemia and very serious conditions where a very good, fast-acting drug is needed.

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GOOD LUCK ☺