Medical Committee
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PHARMACOLOGY

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SHEET

SLIDES

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اللهمّ علّمنا ما ينفَعُنا، وانفَعنا بما علّمتنا (:

Aminoglycosides & an Introduction to DNA Synthesis Inhibitors

As the title implies, we'll finish our talk about Aminoglycosides (PROTEIN SYNTHESIS INHIBITORS), and continue with DNA SYNTHESIS INHIBITORS.

Note that this is the last lecture in talking about Antibiotics.
Pay attention and consider some coming parts as a revision ☺

- FIRST; AMINOGLYCOSIDES

We've been talking lately about Aminoglycosides discussing how important it is to keep them in your clinic as a doctor, since hospitals are full of strong Gram-ve bacteria and we need such drugs to cover a wide spectrum of them, meaning they're still good antibiotics to be used against Gram –ve bacteria.

We start looking for Aminoglycosides (e.g. Gentamycin) after long periods of abusing and misusing certain drugs like the drugs of the 3rd and 4th generations of Cephalosporin, Carbapenems, and Piperacillin.

We brought Aminoglycosides back to clinics to use them against the growing resistance (mainly of E.COLI, PSOUDOMONAS, and ENTEROBACTER) to previously mentioned misused drugs. Also we're facing problems with almost all microorganisms including Serratia and Proteus.

Written by Amani Al Halabi

- Some points would briefly summarize the **clinical uses** of Aminoglycosides:

1- With cases of **Septicemia**, **Pelvic and Abdominal Sepsis (like Peritonitis)** which is usually related to anaerobes or Gram-ve bacteria. BUT here we need to know that:
using of Aminoglycosides is to some extent restricted to certain cases, one of the cases as we mentioned: SEPTECEMIA, in Septicemia we use it for a long time with patients who are infected with E.coli, Enterobacter, or Pseudomonas, and didn't really show good clinical responses upon using drugs of 3rd of 4th generations of Cephalosporin or Carbapenems, SO THAT here we're able to give GENTAMICIN, although it's a very confusing decision but we have to make it in such life threatening situations.
- It's not an everyday-used drug to treat Septicemia. An everyday drug for Septicemia should cover many Gram-ve bacteria and be associated with less harmful side effects (e.g: Cefepem, Imipenem, or Piperacillin with tazobactam (tazocin –the combination of both antibiotics-)), and If I'm at the hospital and afraid of MRSA, I have to add Vancomycin.

→ A short conclusion: we use Aminoglycosides - gentamicin for example- in cases of no response to other drugs, or if a result of culturing shows that a certain microorganism is no longer susceptible to a usual drug, and the drug isn't active against it anymore.
An example: Cases of Pneumonia or Klebsella where the patient isn't responding to Moropenem nor Imipenem.

2- Commonly, in low doses, with bacterial **Endocarditis** cases, caused by enterococci, streptococcus, or staphylococcus species.

Remember, we previously used Ampicillin in cases of enterococci infections (endocarditis), if these enterococci aren't susceptible to Ampicillin, or if the patient suffers from penicillin allergy then we switch to Vancomycin. But are those 2 antibiotics really enough?
Some times you need to add GENTAMYCIN to Ampicillin or to Vancomycin forming new effective drugs mainly against endocarditis:
GENT-AMP & GENT-VANC combinations. (These combinations are mainly used in the treatment of endocarditis).
Note: enterococci and some other organisms that cause endocarditis aren't susceptible to Aminoglycosides alone (even Gram+ve aren't susceptible to Aminoglycosides, by the way, except few staphylococcus bacteria), while

when we add Aminoglycosides to Penicillins we end up with a synergized effect against enterococci. -Similar synergized effect isn't scientifically based with Cephalosporines but Ceph-Gent combinations may still be used-

NOTE: For PROPHYLAXIS against endocarditis:

- Oral amoxicillin: (2 grams) before dental surgeries in communities where enterococci are sensitive to penicillins.
- Injectable ampicillin: in serious situations where the patient is unconscious for example.
- Injectable vancomycin: where enterococci aren't sensitive –resistant enterococci-, as in the USA

★ GENTAMICIN is NOT used for prophylaxis!

Let's move to
3- **PNEUMONIA**, the nosocomial, not the Community Acquired types.
(CAP is caused by "nice" and simple organisms; Strep, Staph, H. influenza, Mycoplasma, and Liogenella).

- BUT what are the main causes of <u>HOSPITAL AQUIERD PNOUMONIA</u>?

a) Pseudomonas Aeruginosa (40-45%) b) MRSA (20%)
c) H. Influenza d) E.coli e) some enterobacter species

→ the big issue is related to the PSEUDOMONAS Aeruginosa. It, by nature, has some sort of RESISTANCE ☹, it's not susceptible to a single therapy!

* TREATMENT:
-Here we **can't** use Azithromycin nor Azithromycin + Vancomycin because they don't cover PSEUDOMONAS!
Then how to cover Pseudomonas? PIPERACILLIN, CEFTAZIDIME, CEFOPERAZONE, IMIPENEM, MEROPENEM, AZTREONAM, and AMINOGLYCOSIDES.

- → Here we'll use a different mechanism of action because Pseudomonas is really a very bad infectious agent. We'll use a **combination** of antibiotics.
(Remember; against resistant H.Pylori, we use a combination of a Protein synthesis inhibitor and a cell wall synthesis inhibitor: Clarithromycin + Augmentin (Amoxicillin))

ANDDD the same applies here, we'll form a combination of two different drugs (different drugs = **not** two cell wall synthesis inhibitors for example = not cefoperazone or ceftazidime + piperacillin!)

→ we'll combine a protein synthesis inhibitor (Gentamicin, Amikacin, or Tobramycin) with a cell wall synthesis inhibitor (any of them would work starting from ceftazidime and ending with meropenem, but remember that we prefer the narrowest, it's better; usually we use cefepime).

The doctor here went back to the slides and read: Although supportive clinical data are lacking for superiority of combination therapy over single-drug therapy, because of the propensity of P. Aeruginosa to develop resistance during treatment, an anti-pseudomonal penicillin is frequently used in combination with an aminoglycoside or fluoroquinolone for pseudomonal infections outside the urinary tract.
[Outside the urinary tract = we're talking mainly about Pneumonia]

A Question: Does this have any clinical or theoretical support?
Actually no, it doesn't, but it's considered a part of the guide lines in the medical world; WHNEVER YOU ARE DEALING WITH PSEUDOMONAS (In Hospital Acquired Pneumonia with green pus) → COMBINE!

4- **Tuberculosis.** [Will be mentioned in RT lectures next year Inshalla]
5- **Brucellosis**: we said we need to give 1 gram, for 1 week, of streptomycin, unless the patient can't tolerate it, we'll give hem Gentamicin.
6- **Palgue**. [Don't really care about this]

7) to **sterilize the bowel** of patients who receive immunosuppressive therapy before surgery, & in hepatic coma. EXPLANATION: for patients who are dealing with immunosuppressive agents, there GI tracts are full of microorganisms, (risk of severe infections after a surgery). So we STERILIZE THEIR BOWLES before surgeries by a not absorbable drug [e.g: NEOMYCIN - an aminoglycoside-, a drug that goes through the stomach towards the duodenum and sterilizes the bowels].
Another case in which we use sterilizers; Liver Cirrhosis; where released AMMONIA from good microorganisms in the GI isn't anymore detoxified by the liver and it travels through the blood and accumulates in the brain causing: Hepatic encephalopathy (Hepatic coma).

FOR THAT we need to get rid of these microorganisms and keep them at low numbers, thus low concentration of Ammonia to prevent more progression of the case by NEOMYCIN [oral, 500mg].

8) Used in infected **burns**, **otitis externa**, acute **pyelonephritis .** ***in actual clinical practice, we don't really use Aminoglycosides for such cases anymore.****

9) Amikacin is the Broadest (Widest) antibacterial spectrum preferred in **serious nosocomial G –ve bacillary infection** in hospitals where Tobramycin & Gentamicin have developed resistance. [We can obtain the level of resistance from certain statistics and charts.]

Here's a real related **story**: Dr. Asem with a Master degree student isolate 150 specimens to test the sensitivity of E.coli in patients who are admitted to the hospital, there were the surprising results that 47% of E.coli is resistant to Gentamycin and Tobramycin, 98% of it is resistant to Ampicillin, 77% is resistant to Ceftriaxone, So Please Learn, as books say, to prescribe drugs according to the regional spectrum and the resistant bacteria in the certain hospital.

10) They are effective in the empirical treatment of **infections suspected of being due to aerobic gram-negative bacilli**.
10- Neomycin is reserved for **topical applications** because of their systemic toxicity.

FINAL QUICK NOTES ABOUT AMINOGLUCOSIDES:

- Aminoglycosides are not absorbed from the GI tract.
- They are usually administered intramuscularly or intravenously.
- Serious dose-related side-effects occur with the aminoglycosides, The main hazards are **nephrotoxicity** and **Ototoxicity.**
- **Ototoxicity**: (Accumulation of them causes balance disturbances, inhibition of protein synthesis in cells of VESTIBULA, Necrosis, and Loss of hearing).
- We used to monitor troughs and peaks while using Vancomycin, and here we HAVE TO monitor them also when we're dealing with Aminoglycosides. Keep an eye on your patient!
- Although they are bad drugs that cause Oto- and Nephro- toxicity, we still need them to fight the growing resistance of Gram-ve bacteria, and in combinations to treat Pseudomonas in hospital acquired Pneumonia, certain previously mentioned cases of Septicemia.

→ Won't talk more about Aminoglycosides, Ignore Clindamycin temporarily, and head for a new group of drugs:

DNA SYNTHESIS INHIBITORS [DNA Gyrase Inhibitors]

Quinolones::

- A nice effective group, why? They are **ORALLY** taken antibiotics, with a very good activity on **GRAM-VE** bacteria. [Note that Aminoglycosides aren't taken orally].
* ASK → Is there any other drug that's taken orally and effective against Gram-ve? Yes, CEFDINIR, but it wasn't discovered yet.

- The first discovered one: **CIPROFLOXACIN –a fluoroquinolone-**

- A special type of antibiotics that work on what's called: GYRASE ENZYME, an enzyme that functions in cutting supercoils of unzipped DNA, then rejoin the separate ends at the sides of the removed coil.

* ASK → So how do Quinolones inhibit this enzyme? At the time the Gyrase cut the coil of DNA, Quinolones bind to it (trap it) preventing it from rejoining the cleaved DNA → Forming what's called: **CLEAVABLE COMPLEX** [Drug+ Gyrase+ Cleaved DNA] → Expressing a **BACTERICIDAL** effect. For that reason we call it **POISONS** of the cell.

* That was the right and precise description of the mechanism of action of these drugs, not as mentioned in books and slides where they say: Inhibition of DNA gyrase prevents the relaxation of positively supercoiled DNA that is required for normal transcription and replication.

- It's a broad spectrum antibiotic, active against both Gram-negative (a lot) and Gram-positive bacteria (not that much). It is more active against Gram-negative species. Also active against other types like: Mycoplasma & Liogenella, [and here remember MACROLIDES] ☺ → Means they cover some causative agents of CAP [just some types due to the fact that they don't cover all Gram+ve bacteria].

DETAILED SPECTRUM:

- CIPROFLOXACIN spectrum **includes all Gram-ve bacteria including Pseudomonas**, does **not** cover H. Influenza, and **poorly** cover streptococcus pneumonia (not good coverage)!
so it's not used to treat upper RTIs nor lower ones

→ It's (Ciprofloxacin) the drug of choice in all **E.coli infections**, including complicated **UTI**s, **Gastroenteritis** [bacterial diarrhea caused by Shigella, salmonella, E. coli.], **Cervicitis** [long treatment]**, and Prostatitis** [where treatment lasts for around 40 days]**,** and these are very common here in Jordan.
* can be used as prophylactic drug with ladies who commonly develop UTIs*

- RESPIRATORY QUINOLONES:

Modified quinolones, aim for improving the Gram+ve coverage to include Strep and Staph species.

* 3 drugs: **Levofloxacin, Moxifloxacin and Gemifloxacin**
***Levofloxacin**, with a trade name: MATADOR.
*it covers all Gram-ve, all Gram+ve (strep+staph), Mycoplasma, h. influenzae, chlamydia, legionella, Pseudomonas, E.coli, Serratia, Shegella, Salmonella, and Proteus.
*Effective and used increasingly for treatment of **upper and lower respiratory tract infections.** Also effective in #UTIs and #Gastroenteritis but we don't usually use it here for its wide spectrum. (in # we stick to Ciprofloxacin for its narrow spectrum)
*So-called respiratory fluoroquinolones, have enhanced gram-positive activity and activity against atypical pneumonia agents [e.g: chlamydia, mycoplasma, and legionella]

Note: all 4 drugs (Cipro, Levo, Moxi, Gemi) cover gram-ve including pseudomonas A, ASK → Can we combine them with cell wall synthesis inhibitors in treating cases of hospital acquired Pnuemonia? Yes indeed, and we commonly do that, (mostly cipro with a cell wall synthesis inhibitor).

QUICK NOTES:

• *in Post-treatment of UTIs, we may face recurrent infections (3-4 repeated infections/year) and here we treat then apply a prophylactic agent for a long time (6months – 1 year) with a half dose of Ciprofloxacin or another drug that will be mentioned later on.*

• *Both Quinolones and aminoglycosides are bactericidal, but Aminoglycosides are* ***faster*** *than Quinolones, because aminoglycosides cause membrane disturbances and quinolones need to penetrate the cell before reaching the DNA and cutting it.*

• *First oral antibiotics effective against gram-negative bacteria.*

• *Ciprofloxacin is the most commonly used fluoroquinolone.*

• *Ciprofloxacin most active agent against gram-negatives, Pseudomonas Aeruginosa in particular*

• *Levofloxacin, Gemifloxacin, and Moxifloxacin: improved activity against gram-positive organisms, particularly Strep. pneumonia and some staph. pneumonia.*

ASK → In mild to moderate cases of community acquired pneumonia (90% of the cases) we tend to use Azithromycin or Telithromycin (Macrolides = Bacteriostatic), BUT WHAT TO DO IN CASES OF SERIOUS AND SEVERE Pneumonia? We use Respiratory Quinolones which are Bactericidal and cover all causes of pneumonia [Staph, Strep, Liogenella, Chlamydia, Mycoplasma, H. influenza] but don't use them unless there's a real need, we don't want to lose them.

• Quinolones are also used in infections of soft tissues, bones (Osteomyelitis), and joints and in intra-abdominal infections.
Here we use Ciprofloxacin for 6 months in many cases.
→Keep in mind that Ciprofloxacin is used here for its nice penetration of bones and other soft tissues.

Again in short:
Ciprofloxacin: for treatment of complicated UNI, prostatitis, cervicitis, gastroenteritis (because the causative agents in all of these are mainly gram-ves) and cipro is enough to cover them.
Ciprofloxacin: treatment of Infections of soft tissues, bones, and joints because it penetrates them well.
Respiratory quinolones: (3drugs) mainly in lower and upper RTIs because they include activity against gram+ve bacteria.

SIDE EFFECTS:

- Side-effects are infrequent and usually mild. They consist mainly of **GI disorders** (nausea, vomiting, and diarrhea) and skin rashes –rare-.

- **Arthropathy**:

* In real life time, you commonly meet elderlies (men) that keep complaining from a pain in their knee joints, here you doctors ask them if they're taking statin, if not, then ask a second question: do they take ciprofloxacin? Or in other words do they suffer from Prostatitis and are taking some drugs for that infection? If yes, then we conclude that ciprofloxacin (and flouroquiniolones in general) cause Arthropathy; damage in growing cartilage, particularly in young individuals.
*For that bad side effect, they're contraindicated and can't be given to children under 18 years, they are growing and it will affect their bones causing many problems and hypoplasia.

*It really cause Arthropathy in Prostatitis patients because they use these drugs for long time (up to 40 days) and this long use results in accumulation of the drug in the body.

* Whenever we stop using the drug, the pain starts to fade, it's a reversible effect.

* Ciprofloxacin shouldn't be given to pregnant ladies because it may affect the fetus.

A final random note: augmentin can be given empirically but NOT amoxicillin, if any previous sheets contradict this, please correct them.

THE END

~ على قَدْر أحلامنا تتّسعُ الأرض ~

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