Medical Committee
The University of Jordan

PHARMACOLOGY

Lecture No.: 33

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SHEET ■

SLIDES □

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Miscellaneous antibiotics & Antivirals

A message from the doctor:

The spectrum of each antibiotic is not required. Pharmacology course is concerned with drugs, their uses, and their adverse effects. You will not be asked about spectrums in the exam. Try to know the drug of choice for the infections and diseases that we discussed earlier.

The final exam is going to be as easy as the midterm exam.

In this sheet we will be covering:

- Quick note about quinolones.
- Sulfonamides group and Cotrimoxazole.
- Teicoplanin.
- How to treat Vancomycin resistant enterococcus (VRE).
- Clindamycin.
- Introduction to antivirals.
- Aciclovir.

Quinolones

We finished last lecture by showing the side effects of quinolones, and the last thing we said was: respiratory quinolones are contraindicated in children under 18 years of age except in special cases. One of those special cases is **cystic fibrosis**.

Cystic fibrosis: a genetic disorder that affects mostly the lung but also the pancreas, liver, and intestines. Chronic respiratory infections are very common in cystic fibrosis patients. Here, we use respiratory quinolones, even in children under 18.

So what you need to know is: quinolones use in children is not absolutely contraindicated. We give respiratory quinolones to children in cases of cystic fibrosis.

Sulfonamides

Sulfonamide is the basis of several groups of drugs. Antibacterial sulfonamides have been used in the past in treating infections but are no longer being used except that there is a new entry to sulfonamides, a sulfonamide containing drug called **co-trimoxazole**.

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Antibacterial sulfonamides are **bacteriostatic**; they inhibit growth and multiplication of bacteria, but do not kill them.

Sulfonamides affect the DNA and the building up of nucleotides (that's why they're called antimetabolites) by inhibiting folic acid synthesis, an important metabolite for building up purines.

Two ways to inhibit the building up of purines:

1) All sulfonamides inhibit the enzyme **dihydropteroate synthetase**. Thus, they inhibit the synthesis of the bacterial folic acid, and the end result is interfering in nucleic acid synthesis. Humans, in contrast to bacteria, acquire folate through the diet therefore not affected by sulfonamides.
2) **Trimethoprim** (not a sulfonamide) inhibits the enzyme **dihydrofolate reductase**.

   These enzymes are needed to build up nucleotides for the synthesis of DNA. If the cell cannot build purines, it cannot replicate.

Most of the microorganisms are becoming resistant to sulfonamides. This is why we use a dual-effect: two drugs in the same tablet.

Example on a dual-effect is: **co-trimoxazole**. It consists of: **Trimethoprim** and **Sulfamethoxazole**, and abbreviated as (TMP-SMZ)

Trimethoprim	Inhibits dihydrofolate reductase
Sulfamethoxazole	Inhibits dihydropteroate synthetase

Trimethoprim-Sulfamethoxazole (TMP-SMZ) **clinical uses:**

1) Urinary tract infections and prostatitis. (the most important application for this drug) TMP-SMZ has a very nice activity against gram-negative and *E.coli.*
2) Pneumocystis pneumonia (PCP) or pneumocystosis caused by a fungus called *Pneumocystis jirovecii.* This infection is seen in immunocompromised and elderly patients.
3) Prophylaxis of recurrent urinary tract infections.

Teicoplanin

Teicoplanin is from the same family as Vancomycin (glycosides) , and both are protein synthesis inhibitors.

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Teicoplanin is mainly used in prophylaxis and treatment of serious infections caused by Gram-positive bacteria, including MRSA and *Enterococcus faecalis* causing endocaditis

When treating MRSA, we prefer to use Teicoplanin instead of Vancomycin in patients who:

A. Suffer from renal problems.
B. Are very young babies (days), since it's less likely to cause nephrotoxicity.

Usually if the microorganism is resistant to Vancomycin, it is probably resistant to Teicoplanin as well.

How to Treat Vancomycin Resistant Enterococcus (VRE)

If you start to treat a patient (that has for an example endocarditis caused by enterococci/or MRSA linked pneumonia/ or septicemia…etc.) with Vancomycin and the patient does not respond. What do you use?

We introduce new drugs that are effective against MRSA & VRE which are:

A. Linezolid
B. Daptomycin

Linezolid

- ✓ Effective against VRE faecium.
- ✓ Used for community acquired pneumonia and nosocomial pneumonia.
- ✓ Should be reserved for treatment of infections caused by multidrug resistant gram positive bacteria. (Keep it for the future)

Daptomycin

- ✓ Effective against VRE and *Staphylococcus aureus.*
- ✓ Not a good choice for respiratory tract infections caused by MRSA or VRE. Why?
  Daptomycin is hydrolyzed within the respiratory tract because of the respiratory secretions.

What you need to understand is that there are alternatives for Vancomycin and those are used for one the following reasons:

1) Nephrotoxicity caused by Vancomycin → we use Teicoplanin.
2) Resistance against Vancomycin → we use Linezolid or Daptomycin (but not in respiratory infections).

Clindamycin

Whenever you face the antibiotic Clindamycin remember: **anaerobes**!

Where are anaerobes? Oral cavity.

Uses

1) Serious oral cavity infections.
   Simple infection → Penicillin V
   Serious infection → Clindamycin (its commercial name, Dalacin C)

2) Aspiration pneumonia: pneumonia caused by anaerobes.
   Aspiration pneumonia is usually caused by incomplete swallowing (تشردق), what happens is; some anaerobic bacteria coming from the oral cavity reaches the lungs producing lower respiratory tract aspiration pneumonia. Drug of choice in this case is: Clindamycin.

   If the physician is not certain whether it is aspiration pneumonia or community acquired pneumonia, he/she should combine Clindamycin with a drug that covers community acquired pneumonia.

3) Acne.
   Clindamycin is being used as a lotion antibiotic to treat acne. However, this lotion sometimes causes a burning sensation.

   Types of pneumonia we came across:
   1. Typical community acquired pneumonia, in children.
   2. Atypical community acquired pneumonia, in adults. Caused by Mycoplasma, Chlamydia, and Legionella .
   3. Hospital acquired pneumonia.
   4. Pneumocystis pneumonia.
   5. Aspiration pneumonia.

THIS IS THE END OF ANTIBIOTICS!

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ANTIVIRALS

Revision of the common infection pathway of any virus (in most of the cases):

1) Adsorption: the virus links to the receptor on the cell.
2) Penetration.
3) Uncoating.
4) Protein synthesis which needs RNA polymerase for transcription.
5) DNA synthesis using viral DNA polymerase.
6) Packing the DNA within a capsule.
7) Release.

In pharmacology, we want to intervent with a drug to inhibit one of the processes above.

Viruses have different properties so we'll group them according to their similarities. Today we'll be talking about the antiviral drugs that treat herpes viruses:

- ✓ Varicella-zoster virus (causes chickenpox).
- ✓ Herpes simplex (causes herpes labialis (oral herpes), genital herpes, & herpes encephalitis).
- ✓ Cytomegalovirus.

Keep in mind

- ❖ The usage of antiviral drugs does not really cure the infection. It usually reduces the duration of the infection by 1-2 days. Because the infection is already spread out. So, the physician has to balance between the cost and the benefit for the patient in addition to the drug's side effects.
- ❖ Usually we don't treat viral infections. However, in some cases we have to treat them e.g. chickenpox in adults.

Aciclovir

- Aciclovir is the most commonly used drug to treat viral infections caused by herpes viruses.
- It is an antimetabolite antiviral, meaning it inhibits the synthesis of DNA.
- Aciclovir resembles nucleosides, they look like A or T or C or G (notice the structure in the slides).
  *Recall that the difference between a nucleoside and a nucleotide is a phosphate.

- These Antimetabolites (like Aciclovir), act as false nucleosides, when incorporated within the viral DNA, it blocks the continuation of replication, blocking transcription, so the virus cannot replicate anymore and this is called **chain termination**.
- What happens actually is that viral polymerase thinks that this is a true nucleoside, it incorporates in into the DNA and stops the transcription because it is not an actual nucleotide.
- What is so special about aciclovir? SELECTIVITY.
- Before Aciclovir, we had a problem with selectivity. The virus gets in the cell and hijacks its machinery, the only solution to get rid of the virus is to kill it, the problem is that if the drug is not selective, it is going to kill replicating cells as well.

- To appreciate the importance of aciclovir, we are going to compare it with older antivirals.

Other antivirals مش حفظ فوق عاليمين بالسلايد- الاسماء	**Aciclovir**
All of them are **nucleoside-like**, to become **nucleotide-like** and interfere with the viral DNA, three phosphate groups have to be added to these structures by the enzyme **kinase**.	
Old generations depend on the **cellular kinase** of the host, meaning it will inhibit the viral DNA polymerase and the human DNA polymerase specially in replicating cells (such as bone marrow).	Aciclovir is only recognized by the **viral kinase**, meaning aciclovir is only activated in infected cells and will inhibit the viral DNA polymerase and not the human DNA polymerase. * aciclovir is 30 fold more potent against viral enzymes than host enzymes.
Toxic to replicating cells of the host causing bone marrow suppression (very bad)	Non toxic No side effects for aciclovir
No longer used	Very commonly used

Note: this kinase's selectivity is only observed in the kinase that mediates the **initial phosphorylation step** which turns the X nucleoside into an X-monophosphate. The remaining two steps are mediated by cellular kinases in both aciclovir and the other group of antivirals.

** Aciclovir is active against: Herpes simplex, Varicella-zoster, & Cytomegalovirus.
** Rapidly broken down in cells.
** Orally active and non-toxic systemically
** Is there a resistance for aciclovir? Yes, there is. But not very common.

Resistance against aciclovir develops in two ways:
1) Decreasing the activity of viral kinases.
2) Altering DNA polymerase.

Aciclovir by is turned to aciclovir monophosphate by thymidine kinase (viral kinase), then by cellular kinase it's turned to aciclovir triphosphate, it goes to DNA, gets incorporated there and terminates the synthesis.

** Aciclovir has a very bad bioavailability due to first pass metabolism; only 15-20% of the drug reaches the systemic circulation after oral administration. This affects the dosing and frequency of administration (usually taken 400 mg, four times a day).
One of the solutions for this problem is to protect it against the first pass effect. How?

Valaciclovir

Valaciclovir is a prodrug, activated in the liver. By this drug, bioavailability increases from 20 to 60%. So we can decrease the dose and frequency of administration (twice a day instead of four times a day, and in lower concentrations).

Uses:

1. Treatment of
   A. Herpes simplex infections
   B. Genital herpes
   C. Oral labialis
   D. Herpes encephalitis
   Note: herpes encephalitis is a serious condition, so we need to inject aciclovir instead of giving it orally to achieve a really high bioavailability.

2. Prophylaxis in patients with recurrence of genital herpes or oral labialis (if the infection happens more than three times a year).
   Note: this prophylaxis is **not to eradicate the virus**, but to **decrease the load**.
   A study showed that 85% of individuals have latent herpes simplex virus in their saliva, and whenever the immunity is affected, those latent viruses give rise to infections.
   For an example during stressful conditions, people experience mouth ulcers, because immunity is suppressed and those viruses are present in the oral cavity already. Oral labialis does not really have to be treated; treatment of this infection will only reduce the duration of infection by one day which is not really beneficial.

3. Treatment of chickenpox caused by Varicella-zoster especially in adult patients. In children we don't really treat it but in adults it is really difficult and has to be controlled.
   We only give aciclovir to treat chickenpox for children who are under 1 year since they're not yet vaccinated, the live attenuated vaccine is given at 1 year of age.

4. Prophylaxis in immunocompromised patients for e.g.: transplant patients, Aids patients, or patients who are being treated with anticancer drugs. Because those patients are in danger to get infected with latent viruses.

** Common side effects of Aciclovir/Valaciclovir:

- Nausea.
- Diarrhea.
- Vomiting.
- Headache. (1-3% of the population)

** Common side effect of Aciclovir administered IV (in herpes encephalopathy):

- Nephrotoxicity.

This is more common when aciclovir is given as a rapid infusion and in patients with dehydration and preexisting renal impairment. Adequate hydration (using normal saline, 1-2 liters daily) which accelerates the excretion of the drug outside the body, a slower rate of infusion, and dosing based on renal function may reduce the renal toxicity of drugs. We use this with aciclovir, cyclosporine and cisplatin.

THE END