PHARMACOLOGY

◉ Sheets ○ Slides

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Subject: Antibiotics & Introduction to Antivirals

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In the previous lectures, the following points were tackled:

- ✓ Differentiation between different protein synthesis inhibiting antibiotics
- ✓ Recognizing different clinical uses of antibiotics
- ✓ Outlining notable side effects of some antibiotics
- ✓ Importance of identifying the spectrum of antibiotics for efficacious clinical use.
- ✓ Monitoring the level of certain antibiotics in blood by measuring concentrations at the peak and trough

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Antibiotics

Clindomycin

- ❖ **Clindomycin**[1] is an antibiotic with an activity against anaerobes + gram positive bacteria (Staphylococci and Streptococci). It is similar to cefazolin and cefuroxime and used for skin infection but Clindomycin covers anaerobes as well.

- ❖ **Clindomycin** is mostly prescribed by dentists because it covers anaerobes above the diaphragm (anaerobic bacteria in the mouth). In addition, dentists may prescribe Penicillin V. Dentists should not prescribe Augmentin immediately. They should consider prescribing either Clindomycin or Penicillin V.

- ❖ Aspiration Pneumonia is an inflammation (due to an infection) of the lungs and bronchial tubes that takes place after inhaling foreign matter. It is also known as anaerobic pneumonia. This condition is caused by inhaling materials such as vomitus, food, or liquid. *In aspiration pneumonia, anaerobic bacteria from the mouth enter the lung*. **Clindomycin is used in this case.**

- ❖ Clinical Application:

  During surgeries, anesthesia (*used to induce unconsciousness during surgery*) and intubation (*which is the placement of a flexible plastic tube into the trachea to maintain an open airway or a channel to administer drugs*) cause relaxation of muscles. After surgeries, patients need time to regain the reflux action (of the respiratory tract) so they are more prone to inhaling foreign and bizarre objects such as small chicken bones or pins. As mentioned previously, inhaling foreign matter causes aspiration pneumonia.

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[1] It can be written either Clind***o***mycin or Clind***a***mycin.

- In 1973, a patient took Clindomycin and got pseudomembranous colitis. The patient died afterwards. *It was assumed that clindomycin was the prime suspect in this case*. However, in reality, **clindomycin does not cause pseudomembranous colitis.** In general, other antibiotics may cause pseudomembranous colitis because they disrupt the balance between the healthy and harmful bacteria. In fact, antibiotics tip the balance in favor of *Clostridium difficile*, which is a harmful bacterium that causes pseudomembranous colitis.

Quinolones

- **Quinolones** are an excellent class of antibiotics that have a good activity against gram negative bacteria.
- **Quinolones** can easily penetrate through tissues to reach the urinary tract to combat urinary tract infections.
- Unlike most antibiotics, quinolones have a decent activity against the following bacteria:

    1. E. coli
    2. Salmonella
    3. Shigella
    4. Pseudomonas
    5. Proteus

- Gastroenteritis is caused by E. coli, salmonella, or shigella bacteria. The drug of choice for treating gastroenteritis is fluoroquinolone.
- 95% of urinary tract infections in Jordan are caused by E. coli. The drug of choice for urinary tract infection is also fluoroquinolone.
- Moreover, quinolones are used to treat prostatitis and cervicitis.
- The old generation of quinolones has a good activity against gram negative. They also have an adequate activity against Staphylococci.
- The old generation of quinolones (1st) includes **Nalidixic acid**.
- **Ciprofloxacin** is the drug of choice for treating all types of urinary tract infections, prostatitis, cervicitis and gastroenteritis.
- The new generation of quinolones (2nd) includes ciprofloxacin
    - The 3rd generation is called respiratory quinolones. **Respiratory quinolones** have a fine activity against bacteria causing respiratory infections such as: *Streptococcus pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

- Respiratory quinolones (3rd generation) include levofloxacin, gemifloxacin, and moxifloxacin.
- Levofloxacin's proprietary name (brand/trade name) is Tavanic.
- Levofloxacin is nicknamed the "matador" because it is a very powerful antibiotic.
- **Respiratory quinolones** have enhanced activity against gram positive and atypical pneumonia agents (like chlamydia, mycoplasma, and legionella bacteria). They are very effective, therefore, used progressively more for the treatment of upper and lower respiratory tract infections.
- **Respiratory quinolones** are <u>bactericidal</u>.

<u>NOTE:</u>

If a patient has community acquired pneumonia and <u>does not need</u> hospitalization, **azithromycin** is administered.

If a patient has community acquired pneumonia and <u>needs</u> hospitalization, Tavanic (**Levofloxacin**) is administered because it covers all causes of community acquired pneumonia including: *Streptococcus pneumoniae*, *Legionella pneumophila*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*.

- *Is it possible to administer respiratory quinolones for treatment of upper respiratory tract infections?*
  Yes, but they have a very broad spectrum covering gram positive, gram negative and atypical pneumonia agents (with some activity against anaerobes). Therefore, drugs with narrower spectrums (e.g. Augmentin, cefuroxime, and azithromycin) should be used to maintain the effectiveness of the newly developed respiratory quinolones.

- Respiratory quinolones can be taken orally because they are easily absorbed in the gastrointestinal tract. They can be used in hospitals as injections.

<u>Remember</u>:

- ✓ **Penicillins or cephalosporins** (cell-wall inhibiting antibiotics) are combined with **aminoglycosides** to fight pseudomonas infection.
- ✓ **Ciprofloxacin** can be combined with **aminoglycosides** to combat pseudomonas infection.
- ✓ Ciprofloxacin is not used for respiratory tract infections because it does not cover respiratory tract infection agents.
- ✓ Respiratory quinolones cover all causes of respiratory tract infection.
- ✓ All types of urinary tract infections are treated by ciprofloxacin.

- Bacterial cervicitis treatment takes approximately 3 weeks, while treatment of prostatitis takes 30 days. Treatment of urinary tract infections caused by E. coli takes almost 3-4 days.
- **Ciprofloxacin** is used to treat bacterial diarrhea caused by E. coli, shigella, and salmonella.
- Quinolones are also used, along with other antibiotics, for infections of soft tissues, bones and joints.
- Side effects of quinolones:

    1. Fluoroquinolones may damage growing cartilage and cause arthropathy particularly in young individuals.

        It is contraindicated in children less than 18 years of age except in special cases (like cystic fibrosis). It is also contraindicated in pregnant women.

        If an old patient is complaining from pain in the knee joint, there is a slight chance that it can be due to the use of statin drugs (*Biochemistry link*: statins are drugs prescribed to lower cholesterol levels in blood by inhibiting *HMG-CoA reductase* enzyme) or use of fluoroquinolones (some old men may have prostatitis, which is usually treated by fluoroquinolones).

        Remember that the longer a drug is used, the more side effects patients will have. (3-5 days of use will not result in many or severe side effects. 30 days or more of using the drug, however, may increase side effects.)

    2. Gastrointestinal disorders including nausea, vomiting, and diarrhea are usually mild.
    3. Skin rashes are very rare.

Sulphonamides

- Sulphonamides are a class of antibiotics that inhibit metabolite synthesis.
- Silver sulphonamides are prescribed by orthopedists and dermatologists for treatment of infections.
- Inhibition of Dihydrofolate reductase inhibits purine synthesis and therefore, inhibiting folic acid synthesis.
- Administration of sulphonamides stopped in the 1970s-1980s due to the resistance of microorganisms against this antibiotic.
- Dihydropeptidase, another enzyme, can be inhibited by combination of sulphonamides with different mechanisms of action where one

sulphonamide inhibits dihydrofolate reductase and the other inhibits dihydropeptidase.

- **Cotrimoxazole** is a combination of normal sulphonamide (inhibits dihydrofolate reductase) and a new sulphonamide (inhibits dihydropeptidase). This drug is mostly active against gram negative bacteria.
- If the patient cannot take ciprofloxacin for urinary tract infection for some reason, oral **Trimethoprim-Sulfamethoxazole** is a good substitute.

VRE: Vancomycin Resistant Enterococci

- Remember that vancomycin is used against enterococci.
- If enterococci are resistant to vancomycin, 1 of the 3 following drugs can be used:
    1. **Teicoplanine**: is very similar to vancomycin, however, VRE are still susceptible to it.
    2. **Linezolid**
    3. **Daptomycin**
- **Linezolid** is a very expensive drug used for VRE and VRSA (vancomycin resistant *Staphylococcus aureus*).
- Never prescribe **linezolid** except for VRE and VRSA. It is an alternative for vancomycin when bacteria become resistant to **vancomycin**.

Antiviral Drugs

- Viral replication cycle:
    1. Viruses are adsorbed and attached to receptors on host cells.
    2. Viruses penetrate the host cell.
    3. Viruses are uncoated and released into the cell.
    4. Cellular machinery is hijacked by viruses to generate proteins and virions. This step involves polymerase enzymes which are used to replicate DNA and produce proteins.
    5. Viruses are coated and ready for release outside the cell.
    6. Viruses are released outside the cell.

- The viral replication cycle is essential in Pharmacology due to the fact that drugs developed against viruses target one of the steps of the cycle.
- Antiviral drugs are characterized by specificity. The antiviral drug targets few numbers of viruses because viruses have unique characteristics.
- Varicella zoster virus, cytomegalovirus (CMV), and herpes simplex virus are treated by anti-metabolite antiviral drugs like Acyclovir.
- **Acyclovir** is a false metabolite which needs to be phosphorylated in the body to be active. Its structure is similar to a nucleoside which is a nucleotide but without the phosphate group. The abnormal nucleoside undergoes bio-activation by attached of the phosphate groups.
- **Acyclovir** and most antivirals are safe drugs with no prominent side effects because they undergo activation in infected cells where it preferentially inhibits viral DNA replication.

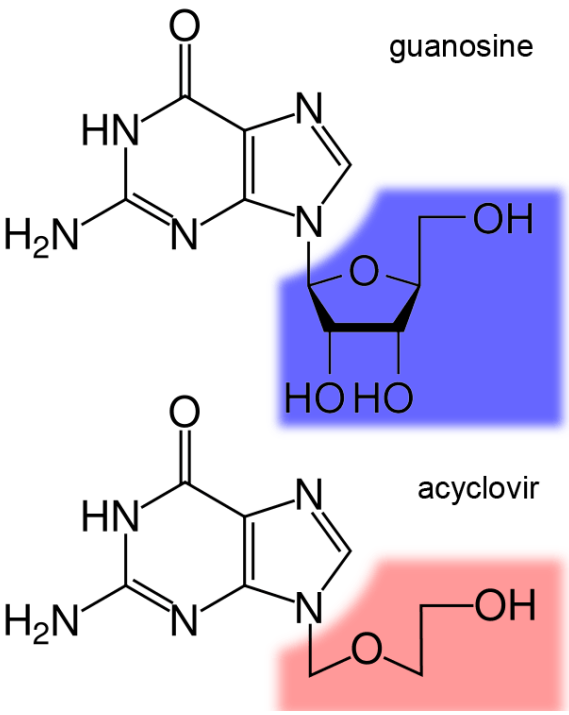

Figure 1 - Acyclovir and Guanosine

- Given that **acyclovir** looks like guanosine (Guanine nucleoside), as shown in Figure 1, it can be incorporated into the DNA by complementary base pairing (C and G). Therefore, replication of the DNA cannot continue and the activity of the polymerase drastically declines.
- **Acyclovir** changes from nucleoside structure to full nucleotide structure by the action of viral thymidine kinase which is a viral enzyme found only in infected cells. This is the reason why acyclovir and most antivirals are safe drugs.
- **Acyclovir** is used in the treatment of herpes simplex, chickenpox, and Varicella zoster infections.

GOOD LUCK!