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بسم الله الرحمن الرحيم

Drugs Used in Genital Infections

Final | Lecture 5

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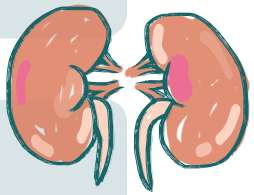
﴿قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ﴾



Drugs Used in Genital Infections

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Metronidazole

- **Metronidazole and tinidazole are nitroimidazoles.** (They contain a nitroimidazole ring).
- They are mainly **active against anaerobic bacteria**.
- Metronidazole is considered the prototype drug of this class and is also effective against several protozoal infections such as, amoebiasis and trichomoniasis.
- **Mechanism of Action:**
- **The nitro group of metronidazole is chemically reduced in anaerobic bacteria and sensitive protozoans.**
- **Reactive reduction products appear to be responsible for antimicrobial activity.**

Metronidazole

Pharmacokinetics:

- The difference between Metronidazole and Tinidazole is that Tinidazole has a shorter treatment duration, and the two drugs are given at different doses.

- **Oral metronidazole and tinidazole are readily absorbed and permeate all tissues by simple diffusion.**
- **Intracellular concentrations rapidly approach extracellular levels.**
- **Peak plasma concentrations are reached in 1–3 hours.**

  Indicating rapid absorption, so intravenous administration is not usually required.

Metronidazole

- **The half-life of unchanged drug is 7.5 hours for metronidazole and 12–14 hours for tinidazole.**

Therefore, Tinidazole remains in the body for a longer period of time, which is why the duration of treatment is usually shorter. Tinidazole is commonly given as a single large daily dose, unlike Metronidazole, which is usually administered three times daily (every 8 hours) for at least 10 days, depending on the type of infection. In contrast, Tinidazole may be prescribed for only about 3 days in some infections because of its longer half-life.

- **Can be given PO, PR** (per rectal)**, Topical & IV.**

Oral and **intravenous** administration are used for systemic infections, while the **rectal route** may be used in complicated amoebic infections involving the rectum. **Topical vaginal** formulations are used for vaginal infections.

Metronidazole

- **Metronidazole and its metabolites are excreted mainly in the urine.**
- **Plasma clearance of metronidazole is decreased in patients with impaired liver function.** Therefore, the dose should be reduced in patients with **severe** hepatic disease.

Metronidazole

- Therapeutic Uses:

1. Bacterial vaginosis: caused by anaerobic bacteria, *Gardnerella vaginalis, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina. The doctor said that you are not required to know the bacterial names; you only need to know that anaerobic bacterial infections can result in vaginal infections (bacterial vaginosis). Usually, these anaerobic bacteria are not normally present in the vagina. The vagina normally contains beneficial lactobacilli, which produce lactic acid and maintain a low vaginal pH, helping to prevent reinfection. Under certain circumstances, anaerobic bacteria can overgrow and replace the beneficial lactobacilli.
2. Trichomoniasis – in the vagina and other places.

Metronidazole

Other therapeutic uses:

A. **Invasive amebiasis in the intestine and liver, but less effective against organisms in the lumen of the gut. They kill the trophozoites of *Entameba histolytica* with no effect on cysts.**
B. **Giardiasis**
C. **Anaerobic bacteria: *Bacteroides fragilis, Clostridium spp &* some** anaerobic oral flora **streptococci. Intra-abdominal infections, Antibiotic- associated enterocolitis and brain abscess.**

For further explanation, see the upcoming slids.

Metronidazole

1. Metronidazole is effective against invasive amoebiasis in the intestine and liver because it kills the trophozoites of *Entamoeba histolytica* present in tissues. However, it is less effective against organisms in the lumen of the intestine because cysts usually reside there, and Metronidazole has little or no effect on cysts.
Therefore, luminal anti-amoebic drugs such as Diloxanide furoate are required to eradicate the cysts from the intestine. Although the cysts may not cause active infection immediately, they can lead to recurrence later, even without re-exposure to contaminated food, due to their persistence in the intestine. For this reason, intestinal amoebiasis usually requires a longer treatment course, commonly about 10 days.
Amoebic infection may invade the intestinal mucosa and spread to the liver, causing an amoebic liver abscess, which is treated with Metronidazole.

2. Giardiasis is usually acquired from contaminated food or water, similar to amoebiasis. However, its treatment is much shorter and simpler. Giardiasis may be treated with a single dose or two doses of Metronidazole; for example 500 mg that can be repeated the next day if needed. In contrast, amoebiasis usually requires higher doses and longer treatment duration, commonly 750 mg every 8 hours for about 10 days.

Metronidazole

3. Anaerobic bacteria such as *Bacteroides fragilis*, *Clostridium* spp., and some anaerobic streptococci can be treated with metronidazole. Some anaerobic streptococci, such as *Peptostreptococcus*, are part of the normal oral flora and may cause infection after procedures such as tooth extraction. These infections are usually anaerobic and require metronidazole or other agents active against anaerobes.

Intra-abdominal and pelvic infections are commonly mixed infections containing both aerobic and anaerobic bacteria, as they often originate from contaminated sites such as the colon in intestinal infections and the vagina in pelvic infections.

Clostridioides difficile infection, which causes antibiotic-associated enterocolitis, can also be treated with metronidazole. Brain abscesses and pulmonary abscesses are usually mixed infections involving Gram-positive, Gram-negative, aerobic, and anaerobic bacteria; therefore, additional antibiotics are often required alongside metronidazole.

Metronidazole

Adverse Effects:

1. **Metallic (Tastes like rust), bitter taste, nausea & dry mouth**
2. **GIT irritation: vomiting, diarrhea**
3. **Irritation of mucous membranes – dysuria, dark urine**
4. **Rash and neutropenia**
5. **Alcohol intolerance: disulfiram-like reaction**
6. **Pancreatitis**
7. **IV infusion may be associated with seizures and peripheral neuropathy**

Metronidazole

8. **CNS: dizziness, insomnia, weakness, headache, sensory neuropathies, parasthesia, ataxia, encephalopathy, seizures. Use with caution in CNS disease**
9. **Needs dose adjustment in severe hepatic or renal disease**
10. **Better avoided during pregnancy and lactation**

For further explanation, see the upcoming slides.

Metronidazole

Adverse Effects:

1. Metronidazole may cause a metallic or bitter taste, nausea, and dry mouth. Dry mouth can usually be relieved by drinking water or frequent mouth rinsing (مضمضة). However, the metallic bitter taste may become more noticeable after the first few days of treatment, and many foods may taste different or bitter. This may affect patient compliance, especially during long treatment courses such as the 10-day treatment used for amoebiasis or anaerobic infections.
2. Gastrointestinal irritation, including vomiting and diarrhea, may also occur. Some symptoms of amoebiasis itself, such as abdominal pain, diarrhea, nausea, and abdominal discomfort, may resemble the adverse effects of the drug. Therefore, patients should be informed about these expected side effects to improve adherence.
3. Metronidazole may cause irritation of mucous membranes, resulting in dysuria, which refers to painful or difficult urination. The drug may cause irritation at any site it reaches, including the vaginal mucosa after topical intravaginal administration. Dark-colored urine is another possible adverse effect during Metronidazole therapy.
4. Metronidazole may cause rash and neutropenia. Neutropenia is a reduction in neutrophils count, which may lead to a degree of immunosuppression and increased susceptibility to infections.

Metronidazole

5. Metronidazole may cause a disulfiram-like reaction when taken with alcohol. Therefore, patients should be advised to avoid alcohol consumption during treatment with Metronidazole.

7. Intravenous infusion of Metronidazole may be associated with seizures and peripheral neuropathy. IV administration is usually reserved for patients who cannot tolerate oral therapy due to severe gastrointestinal irritation. In amoebiasis, oral Metronidazole is commonly given at a dose of 750 mg three times daily. When given intravenously, it may be administered more frequently, such as every 6 hours. Oral administration delivers the drug directly to the gastrointestinal tract, resulting in higher local concentrations in the intestine, whereas intravenous administration distributes the drug systematically throughout body tissues; therefore, the concentration reaching the intestine may be lower than that achieved with oral therapy.

10. Metronidazole and Tinidazole are not strictly contraindicated during pregnancy and lactation; however, they are avoided if possible due to their adverse effects, which may even affect the breastfed infant during lactation.

Metronidazole

Drug Interactions:

1. It potentiates the anticoagulant effect of warfarin.

Therefore, patients receiving Warfarin may require closer monitoring and temporary dose reduction because Metronidazole can increase the anticoagulant effect and the risk of bleeding.

2. Elimination is accelerated by phenobarbital and phenytoin

through induction of drug metabolism **and inhibited by cimetidine,** which is considered a universal cytochrome P450 enzymes inhibitor, and may increase Metronidazole plasma levels.

3. May increase lithium toxicity.

Clindamycin

Mechanism of Action:

- **Inhibits microbial protein synthesis, by interfering with the formation of initiation complexes, and with aminoacyl translocation reactions.**
- **The binding site is the 50S ribosomal subunit and is identical to that of erythromycin.**

- Clindamycin and Erythromycin have similar mechanisms of action but different antibacterial spectra. Both inhibit bacterial protein synthesis by binding to the 50S ribosomal subunit.
- Clindamycin is mainly active against anaerobic bacteria, whereas Erythromycin is active against many organisms, including atypical bacteria that lack a typical cell wall. However, Erythromycin has weak or limited activity against anaerobic infections.

Clindamycin

Mechanisms of Resistance:

1. **Mutation in the ribosomal receptor site.**
2. **Modification of the receptor by a constitutively expressed methylase.** This enzyme methylates the ribosomal binding site, preventing Clindamycin from binding to its ribosomal target.
3. **Enzymatic inactivation of clindamycin.** Some bacteria produce enzymes that chemically inactivate the drug. These enzymes are different from beta-lactamases.
4. **Gram positive aerobes are constitutively resistant because of poor permeability of the outer membrane.**

- **Resistance to clindamycin generally confers resistance to macrolides,** and vice versa.

Clindamycin

Antibacterial spectrum:

- **Anaerobic bacteria both gram positive and gram negative, including *Bacteroides* sp.**
- ***Gardnerella spp, Prevotella spp, Mobilinincus spp, Megaspahera spp, Sneathea spp* and mixed vaginal anaerobs replacing the beneficial lactobacilli in the vagina.**
- **Many gram positive cocci (streptococci, staphylococci and pneumococci) are sensitive.** However, methicillin-resistant staphylococci are usually resistant.
- **Enterococci and aerobic gram negative organisms are resistant.**

Clindamycin

Clindamycin-resistant bacteria:

- **Enterococci**
- **Aerobic gram negative organisms**
- **GBS strains (group B Streptococci)**
- **Gram-negative anaerobes such as B. fragilis (Bacteroides sp.)**

Clindamycin

Pharmacokinetics:

- **Widely distributed into body fluids and tissues, including bone and placenta and breast milk, except brain and CSF.**

Therefore, it may be used in osteomyelitis but not useful in meningitis. Because it crosses the placenta and is excreted in breast milk, it may cause adverse effects in the fetus and breastfed infant.

- **It penetrates well into abscesses.**

In general, many antibiotics have poor penetration into abscess cavities because of reduced blood supply; consequently, microorganisms within the pus may remain viable and difficult to eradicate. Although clindamycin has relatively good penetration into abscesses, abscesses are usually mixed infections rather than purely anaerobic infections. Therefore, surgical drainage is often required for effective eradication of the infection in addition to antibiotic therapy.

- **It is actively taken up and concentrated by phagocytic cells.**

Sometimes, bacteria may survive even after phagocytosis and subsequently cause reinfection.

A well-Known example is Mycobacterium tuberculosis.

- **It is about 90% bound to plasma proteins.**

Because of this high degree of protein binding, it may displace other highly protein-bound drugs from their binding sites when coadministered, potentially increasing their free plasma concentrations.

- **It is metabolized in the liver, and both active drug and metabolite are excreted in bile and urine.**

Drugs that are excreted in bile may be useful in the treatment of biliary tract and gallbladder infections if they are active against the causative microorganisms, because they can achieve therapeutic concentrations in the biliary system.

For example, in a patient with cholecystitis, culture and susceptibility testing may show that the causative organism is sensitive to a particular antibiotic. However, if that antibiotic is not adequately excreted into bile, it may fail to achieve effective concentrations in the biliary tract and therefore may not successfully eradicate the infection.

Clindamycin

- **t½ ~ 2.5 hours in normal individuals and 6 hours in patients with anuria, but no dosage adjustment is needed in renal failure.**
  Because the drug is primarily metabolized in the liver.
- **Accumulates in severe hepatic dysfunction.**

In renal disease, drug accumulation may occur even with mild or moderate impairment because the kidneys have limited regenerative capacity. In contrast, the liver has a large functional reserve and a remarkable ability to regenerate. Therefore, significant accumulation of hepatically metabolized drugs usually occurs only in severe hepatic dysfunction, when hepatic metabolic capacity becomes markedly reduced.

Clindamycin

Therapeutic uses:

1. **Infections of the female genital tract (bacterial vaginosis, septic abortion and pelvic abscesses)**
2. **Anaerobic infections**
3. **Osteomyelitis**
4. **Lung abscess** and other abscesses. But not brain abscess because it's not cross the brain as we said later.
5. **Infections resulting from fecal spillage (penetrating wounds, surgery on GIT, perforation of a viscus).** These infections usually mixed infections, have anaerobic infection along with other microorganisms.
6. **Aspiration pneumonia, in combination with an aminoglycoside or cephalosporin.** In Aspiration pneumonia needs multiple drugs, one for anaerobic bacteria, because the mouth harbours anaerobic microorganisms like peptostreptococcus.

Clindamycin

Adverse Effects:

1. **GIT irritation: nausea, vomiting, diarrhea.** It's real GIT irritation from this drug. It's so annoying and patient may cease the drug.
2. **Superinfection: diarrhea & pseudomembranous colitis** (mortality rate is 50%) **due to *Clostridium difficile*.**

- When microbicidal flora eradicate, the result is opportunistic infection (غاب القط العب يا فار) when the patient is treated by antibiotics against a large spectrum of bacteria, opportunistic infection will work.
- Clostridium difficile can make simple diarrhea (simple here not little, it means diarrhea without pseudomembranous colitis).

3. **Thrombophlebitis.** After IV administration, irritation in the veins cause thromposis.
4. **Thrombocytopenia and neutropenia.** due to bone marrow suppression
5. **Allergic reactions.**

Antiherpes Agents

- **Used to treat herpes simplex virus (HSV) & Varicella-zoster virus (VZV) infections.**
- **Include: Acyclovir, (and other** similar drugs that are prodrug; after entering the body, they are converted into Acyclovir**).**
- **Is an acyclic guanosine derivative.**
- **It is 10 times more potent** (more effective at lower doses) **against HSV-1 and HSV-2 than VZV.**

Therefore, treatment of VZV requires approximately 10 times the dose used for HSV-1 and HSV-2.

Potency is related to the dose required to produce an effect, not to the efficacy.

Acyclovir

Mechanism of Action:

- **Requires 3 phosphorylation steps** (requires 3 phosphate) **for activation: It is first converted to the monophosphate derivative by viral thymidine kinase** (the first one is inside the virus) **and then to the di- and triphosphate by host cell enzymes.** (the second and third steps occur inside the infected host cell. **The activity of the drug is due to the triphosphate form).**
- **Because it requires virus enzymes first for activation, it is selectively activated, and the active metabolites accumulate in infected cells,** since the second and third phosphorylation steps occur within host cells.

Acyclovir

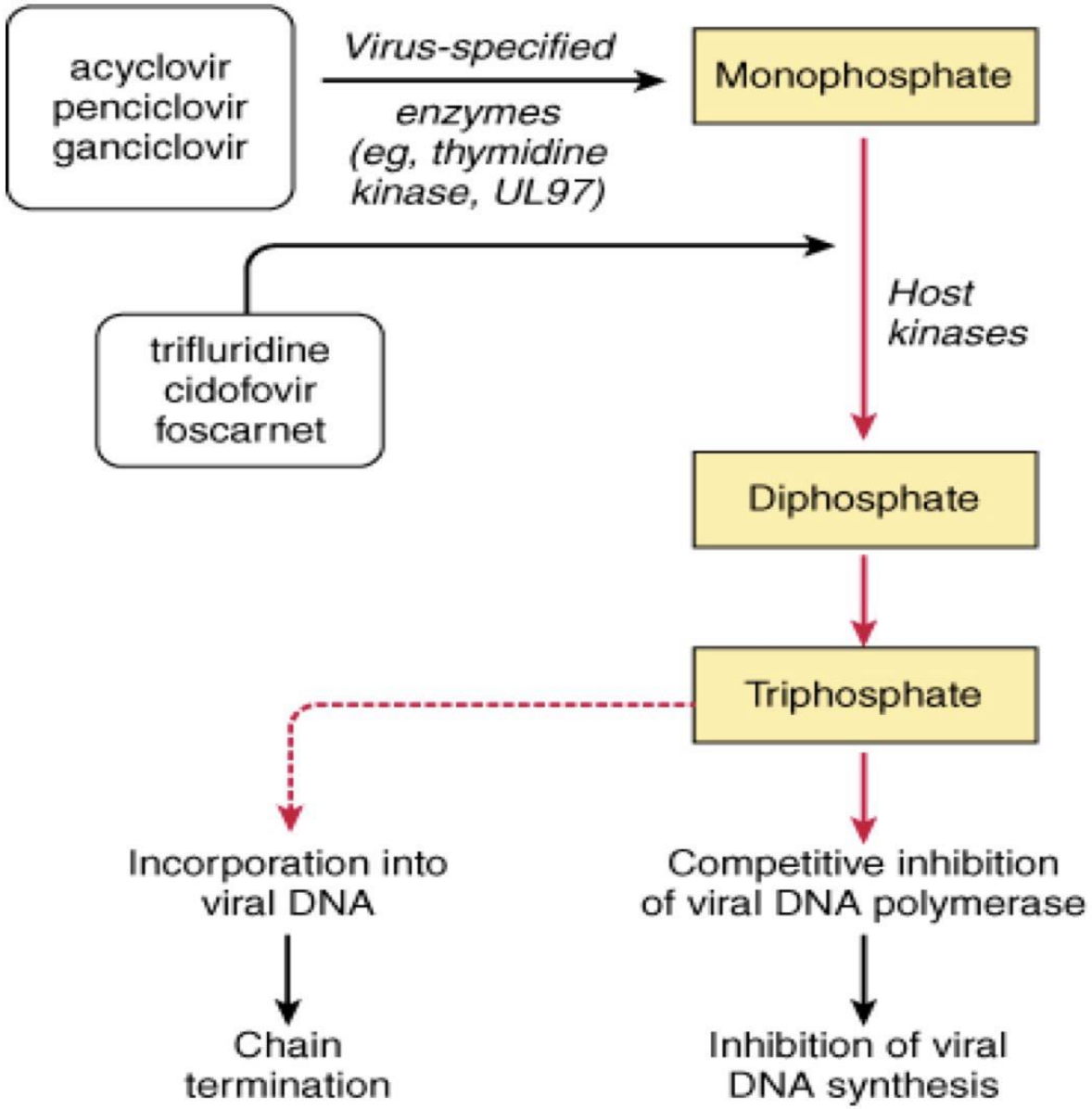
- **<u>Acyclovir triphosphate</u> inhibits viral DNA synthesis by 2 mechanisms:**

1. **Competition with deoxy-GTP for viral DNA polymerase → binds irreversibly to DNA template.** This results in DNA alteration, impairing DNA synthesis and replication.
2. **Chain termination following incorporation into the viral DNA.**

Incorporation of the triphosphate form into viral DNA causes premature termination of DNA chain elongation, thereby inhibiting viral replication.

Mechanism of resistance:

- **Due to alteration** (caused by specific mutations that reduce binding or affinity of acyclovir triphosphate) **of either viral thymidine kinase or DNA polymerase.**



Mechanism of action of antiherpes agents.

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com

Acyclovir

Pharmacokinetics:

- **Bioavailability is low (15-20%)** can be corrected by increasing the dose, **and is unaffected by food.**
- **Available in oral, intravenous, and topical formulations** for HSV, or vaginal.
- **Cleared primarily by glomerular filtration and tubular secretion.**
- **Half-life of elimination is ~ 3 hours in patients with normal renal function, and 20 hours in patients with anuria** (end-stage renal disease).
- **Diffuses readily into most tissues and body fluids.** Which is an advantage for treatment but also contributes to adverse effects.

Acyclovir

Therapeutic uses:

1. **Genital herpes: caused mainly by HSV-2 (although HSV-1 can also be responsible).**
2. **Herpes labialis.**

After a cold or influenza, the patient may notice redness and irritation, followed by the appearance of vesicles. To prevent progression, once the patient feels irritation, they should start using an ointment. However, if vesicles have already appeared, this indicates that viral replication has already occurred.

1. **Herpes zoster.**
2. **Herpes encephalitis.**
3. **Neonatal herpes.**

Acyclovir

Adverse Effects:

1. **Nausea, diarrhea, headache – occasional.**
2. **IV administration may be associated with:**

a) **reversible crystalline nephropathy** due to crystallization of the drug in urine and deposition in renal tissue. Patients should be advised to maintain adequate hydration to reduce this risk.

b) **interstitial nephritis** (hypersensitivity reaction)

c) **neurologic toxicity (tremors, delirium, seizures).**

- **These are uncommon with adequate hydration and avoidance of rapid infusion rates.** Diffusion is a passive process and cannot be actively sped up. However, when plasma concentration is high, the concentration gradient increases, which enhances the rate of drug distribution into tissues.
- **Drug Interactions:**
- **Probenecid and cimetidine decrease acyclovir clearance and increase exposure.** (due to inhibition of active transport mechanisms)

PHARMACOLOGY QUIZ

LECTURE 5

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار،
أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.

عن أبي ذرّ الغفاريّ -رضيَ اللّٰهُ عنه- أنَّهُ سأل رسولَ اللّٰهِ صلَّى اللّٰهُ عليْهِ وسلَّمَ عَن الصَّلاةِ في بَيتِ المقدِسِ أفضلُ أو في مسجِدِ رسولِ اللّٰهِ صلَّى اللّٰهُ عليْهِ وسلَّمَ فَقالَ: "صلاةٌ في مسجِدي هذا، أفضلُ من أربعِ صلواتٍ فيهِ، ولنِعْمَ المصلَّى، هوَ أرضُ المَحشرِ والمنشَرِ، وليأتيَنَّ على النَّاسِ زمانٌ ولقَيْدُ سَوطِ أو قال: قوسِ الرَّجلِ حَيثُ يرى مِنهُ بيتَ المقدسِ؛ خيرٌ لهُ أو أحبَّ إليه مِنَ الدُّنيا جميعًا"

تعاهدوا الأقصى بالدّعاء

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