PHARMACOLOGY

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Subject: Antiviral Drugs -1

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Antiviral Drugs:

Today we'll be talking about the antiviral drugs that treat herpes viruses:

- Varicella-zoster virus (causes **chickenpox** + **shingles**).
- **Herpes simplex** (causes **oral labialis** (oral herpes), **genital herpes** & **herpes encephalitis**).
- **Cytomegalovirus** (the main cause of death in immunocompromised patients, causing **cytomegalovirus pneumonitis**)

1- Acyclovir and Valacyclovir

Acyclovir is the most commonly used drug to treat many viral infections, especially Herpes simplex, and Varicella-zoster.

Pharmacodynamics:

- Acyclovir is a prodrug (must be metabolized by a host enzymes in order to be activated).

- Acyclovir is a **nucleoside analog** (non-phosphorylated nucleotide) that must be phosphorylated by a viral enzyme, *thymidine kinase*. Thymidine kinase is only found in infected cells.

- Phosphorylation of Acyclovir will convert it into a nucleotide that mimics Guanine. So it's going to **inhibit viral DNA-polymerase selectively**. It can also be **incorporated into the DNA** by complementary base pairing (C and G). Therefore, replication of the DNA cannot be continued.

- Resistance against acyclovir develops in two ways:
    1. Decreasing the activity of viral thymidine kinases.
    2. Altering DNA polymerase.
  - The resistance against acyclovir is not that common, only 10% of cytomegaloviruses have built a resistant against it.

Pharmacokinetics:

- Acyclovir has a **low bioavailability** due to first pass metabolism; only 15-30% 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).

- **Valacyclovir** is a prodrug, an esterified version of Acyclovir that has a greater oral bioavailability (from 20 to 60%). It's converted to Acyclovir by first-pass metabolism. By this drug we can decrease the dose and the frequency of administration (twice a day instead of four times a day, and in lower concentrations).

Clinical uses:

Treatment of:

- Herpes simplex infections
- Genital herpes
- Oral labialis
- Herpes encephalitis

1. We can prescribe Acyclovir to treat **genital herpes especially in ladies,** by giving it orally 4 times a day, despite its low bioavailability.

2. **Prophylaxis**:
   - In patients with **recurrence of genital herpes or oral labialis** (if the infection happens more than three times a year).

   - In **immunocompromised patients** (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.

   Note: when we prescribe Acyclovir as a prophylactic drug, the patient should take half of the dose (Acyclovir → 2 dose/day, Valacyclovir → 1 dose/day).

3. Treatment of **chickenpox caused by Varicella-zoster.** Generally speaking**,** we don't prescribe any drug to treat chickenpox, it's a self-limited

infection**. Treatment mainly consists of easing the symptoms** (ex: Paracetamol to reduce fever).

- However, we can use it in life-threatening situations, like **children who are under 1 year** (since they're not yet vaccinated) and **immunocompromised adults**.

- Varicella infection in pregnant women could lead to spread via the placenta and infection of the fetus. This can lead to fetal varicella syndrome. Effects on the fetus can range in severity from underdeveloped toes and fingers to severe anal and bladder malformation. **Here, Acyclovir is the drug to choice to treat these infections.**

4. **Herpes encephalitis** is a serious condition, so we need to inject Acyclovir (IV) instead of giving it orally to achieve a really high bioavailability.

Note: Antiviral drugs must be prescribed before the **flare** of the viral infection (from zero time to 48 hours, i.e. first two days in the infection). Because after that the virus will already have gone so many multiplications, cause remember, anti-viral drugs only work on replicating viruses.

From the slides:

"*Oral Acyclovir has multiple uses. In first episodes of genital herpes, oral acyclovir shortens the duration of symptoms by approximately 2 days, the time to lesion healing by 4 days, and the duration of viral shedding by 7 days. In recurrent genital herpes, the time course is shortened by 1–2 days* "

What does this mean?

- It means that if the patient has a genital herpes, you should treat him with Acyclovir. Usually, genital herpes will take 5, 7, or 10 days to be gone, depending on the infection and its site.

- The Acyclovir here will only shorten the duration of symptoms by **2 days**. But if my patient has a recurrent genital herpes, then treating by Acyclovir is going to lessen the duration by only **1 or 2 days**.

"Oral acyclovir is only modestly beneficial in recurrent herpes labialis."

- In oral labialis you really have to balance between the risk and the benefit, since the drug does not really have a good efficacy for the oral labialis.

- Here, the good doctor will tell his patient I am prescribing you a drug, you are going to take it for 5 days (whether 2 times Valacyclovir/day, or 4 times acyclovir/day), and that drug is going only to reduce the period of the ulcer in your mouth by **1 day**. So after telling him that it'll be the patient's decision if he wants the drug or not. Because the drug here won't have much effect, since it's only going to reduce the period of the ulcer by 1 day.

"Topical acyclovir cream is substantially <u>less effective</u> than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes."

- So there is no cream for genital herpes. Even in oral herpes the effect is modest, not that great.

<u>Adverse effects</u>:

- This drug really causes **nausea**, it's not like the rest of the drugs where they say they cause nausea but actually rarely do.

- In oral Acyclovir, **headache** is happening between 10% of the patients. Moreover, Acyclovir could cause **nausea** and **vomiting** in some patients (5%).

- That's why you have to balance between the risk and the benefit when prescribing this drug. Generally speaking it is a safe drug that does NOT cause bone marrow suppression, which was the old problem of antiviral drugs.

- Additional common adverse effects are when Acyclovir is **administered IV** include **renal insufficiency** and **neurologic toxicity.**

<u>Neurological toxicity?!</u>

- We give **Acyclovir IV** when we want to treat **herpes encephalitis,** but here we have to give high concentrations of this drug in order to reach CNS

(10% of the plasma conc. will reach the brain, so we use higher doses).

- That will allow the drug to enter CNS, treating encephalopathy, but also causing some neurotoxicity.

- These high concentrations will also precipitate in the kidney, causing **renal insufficiency**.

- So how can we avoid those adverse effects when using IV Acyclovir?
  - When you use IV Acyclovir, you have to avoid rapid infusion, by giving it gradually.
  - And you should also hydrate the patient and dilute the drug in saline with every dose, but **why?**
    The idea here that we are giving a dose, raising the plasma concentration; 10% of this concentration is going to enter the CNS, then we hydrate the patient, forcing him to urinate. So the drug which is in the plasma (90%) is going to be excreted, so there won't be a renal insufficiency anymore, and also the drug which entered the CNS will not be affected.

2- Ganciclovir

- Active against all Herpes viruses, and especially Cytomegalovirus (CMV), which is a severe virus that can cause bad **pneumonia**, **retinitis**, **and colitis** in immunocompromised patients.

- The problem is that Ganciclovir produces **bone marrow suppression**, while acyclovir does not.

- Both acyclovir and Ganciclovir are activated through viral thymidine synthase, so both of them should be specific to the infected cells.

- However, in case of Ganciclovir, clinic approved the opposite of that, since it causes several side effects.

- So, it causes bone marrow suppression (leukopenia 40%, thrombocytopenia 20%). In addition, Ganciclovir has CNS effects; headache, which is also

common in Acyclovir, however Ganciclovir is associated with psychosis, coma and convulsions.

- 1/3 of the patients have to stop because of adverse effects. So, why to use it? Because Ganciclovir is very active against CMV (100 times more than Acyclovir), So it is the drug of choice even if it has bad side effects, it is all about risk and benefit balance.

3- Foscarnet

- As we said previously, we treat CMV infections by Ganciclovir. But if the patient is not responding to the treatment, we start treating him by *Foscarnet*.

Pharmacodynamics:

- Foscarnet is inorganic pyrophosphate analog which is a direct inhibitor of **DNA polymerase** (the same target for Acyclovir, however Foscarnet works from a different angle), and **Reverse Transcriptase** (which converts RNA into DNA) that's why the drug is approved for HIV virus.

- The drug is active against Herpes (I, II, Varicella, CMV) including those resistant to Acyclovir and Ganciclovir.

Clinical uses:

- CMV retinitis and other CMV infections instead of Ganciclovir
- H. simplex resistant to Acyclovir.
- HIV

Adverse effects:

- Foscarnet is very potent drug, which can inhibit many viral infections, so why don't we start treating these infections with it?!

  Because it causes **nephrotoxicity** (25%)

4- Treatment of Influenza A & B

- We have four available drugs to treat influenza:
  1- **Rimantadine** and **Amantadine** (attachment inhibitors)
  These two drugs are not used anymore, so forget about them.
  They were used with influenza, then influenza virus built resistance to them, so they're not active anymore.
  Amantadine is also a weak therapy for Parkinson disease.

  2- **Oseltamivir** and **Zanamivir** (Neuraminidase inhibitors)

Pharmacodynamics:

- Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces.

- These drugs are neuraminidase inhibitors, thus inhibiting the release of virions from infected cells, so you need to use these drugs in the first 48 hours in order to prevent the spreading of virions.

- What you won't find in books is when these drugs are actually used, being the only drugs active against influenza right now so guidelines are set for their use. And the WHO put it under highly restriction.

- Oseltamivir and Zanamivir have the same mechanism of action, so if the virus managed to build a resistant against them, we are going to lose our last line of defence against influenza.

- So when should we use neuraminidase inhibitors?
  We should use those drugs when we really need them (in immunocompromised patients, in infants, and in H1N1). So don't use them every time you have a flu.

Pharmacokinetics:

- What's the difference between those two drugs?

  Zanamivir (trade name: Relenza) by inhalation.

  Oseltamivir (trade name: Tamiflu) taken orally.

Note: in 22/12/2014, FDA announced the approval of the antiviral drug **Peramivir**, making an **intravenous (IV) medication available for adult influenza (A&B)** patients who have trouble taking an oral or inhaled antiviral.
So, the third one in this family is **Peramivir**, which is given **IV**.

Effects:

- Administration of neuraminidase inhibitors is a treatment that limits the severity and spread of viral infections, we are not curing the influenza here!

Toxicities:

- Exacerbation of reactive airway disease by Zanamivir, in patients suffering from (COPD, asthma, bronchitis and emphysema).
- Nausea and vomiting for Oseltamivir, but still less than Acyclovir.

Clinical uses:

1. Early administration is crucial because replication of influenza virus peaks at 24–72 hours after the onset of illness.
   When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is decreased by 1–2 days compared with those on placebo, severity is diminished, and the incidence of secondary complications in children and adults decreases.

Note: don't use these drugs except in live threatening situations!

2. The main use for these drugs (Zanamivir & Oseltamivir) is prophylaxis of influenza for immunocompromised patients or doctors that deal with many patients. Once-daily prophylactic effect is 70-90% preventing disease after exposure.

Let's talk now about the story of the new drug **Peramivir ^^:**

In October 2009, it was reported that the experimental antiviral drug Peramivir had been "lifesaving" effective in intravenous treating 8 serious cases of swine flu. On October 23, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization for Peramivir, allowing the use of the drug in intravenous form for hospitalized patients only in cases where the other available methods of treatment are ineffective or unavailable.

The Emergency Use Authorization expired on June 23, 2010. In 2011, they completed phase 3 trails and FDA announced the approval of the antiviral drug **Peramivir** in 22/12/2014

20.5 Antiretroviral (HIV) agents: introduction

- AIDS, Acquired Immune Deficiency Syndrome, caused by HIV virus, it is the meanest virus ever. The history of AIDS tells us that the real name of the disease is Gay-Related Immune Deficiency, GRID. Because the first cases where discovered in the gay community in Texas, and not from monkeys.

- The problem with this disease that it's unbelievably complicated and you can't really cure the patients.

- The only way to stop it is by banishing all patients that are HIV positive, because it can also be transferred vertical (from a mother to her child). In Sub-Saharan Africa the situation is horrible. Also. In the United States the number of AIDS patients is huge, fortunately it's not common in our countries.

- HIV has a very mean enzyme called: *integrase*, which is responsible for combining its genetic material with the chromosomal DNA which is very bad. When the virus infects the cell, it first attaches itself to it (fusion) then it releases its RNA, RT (reverse transcriptase) turns it into DNA and it's double stranded, then this is integrated with the chromosomal DNA in immune cells especially memory cells and won't get out. How we measure it? CDA.

- AIDS is targeted in all the replication steps: fusion, transcription integration, cleavage, release. So many drugs are available; anti-fusion, anti-release, anti-integrase, anti-transcription drugs, anti-packaging and budding, and we must use a combination of all these drugs, in order to prevent the virus from building resistance. Notice that we can't treat it, we only cover it and prolong the patient's life at most 10-15 years.

The end