



Medical Committee  
The University of Jordan



# PHARMACOLOGY

**Lecture No.:** 34

**SHEET**



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## ANTIVIRAL AGENTS

### Acyclovir

A magical, golden drug to treat a viral infection caused by **herpes simplex virus** (HSV-1, HSV-2) and **varicella-zoster virus** (VZV). It is the drug of choice to treat genital herpes, oral labialis, and encephalopathy of herpes.

In herpes encephalitis you need to take the drug intravenously, while in genital herpes and oral labialis you can take it orally (4 times/day). This is annoying, so a new type of acyclovir was introduced, called a **valacyclovir**.

Valacyclovir just a pro-drug, an ester is added to acyclovir making it more bioavailable.

The problem of acyclovir was its poor bioavailability which does not reach more than 20% in the best cases. So that, the usual dose of acyclovir was (600-800 mg, 4 times/day) which is considered a lot, while valacyclovir is enough to be taken (2 times/day).

### Acyclovir Clinical Uses

- In the treatment of genital herpes (orally) , oral labialis (orally) , and herpes encephalitis (IV).
- In treating chickenpox in immunocompromised patients, it depends whether it is a severe case that we may give the drug intravenously, but the oral route is the usual route of administration.
- **The main idea of acyclovir is prophylactic** in patients treated with immunosuppressant drugs or radiotherapy who are in danger of infection by reactivation of latent viruses. A research done on our population found that 85-90% of us have a latent HSV (herpes simplex virus) in the mouth. So when the immune system gets compromised, patients will become susceptible toward latent viruses ,thus infected, so we need to give them prophylactic acyclovir.
- Another main use of acyclovir is **prophylaxis** in patients with frequent **recurrences** of genital herpes. Genital herpes is a big problem for ladies. Thanks God, here in Jordan, we do not really have this problem much because

of our Islam, religion, and morals. We don't have problems of intersexual between people and all of these problems, while in West, it is a big issue, so acyclovir is used a lot as a prophylactic drug.

- Using acyclovir sometimes might be confusing. Let me start reading here:  
“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. **The main point here is that** in recurrent genital herpes, the time course is shortened by 1-2 days.”

What does this mean?

It means in the treatment of viral infection we deal with the situation differently. We are going to prescribe the drugs as doctors telling the patient we are not giving him the magical drug that will cure him tomorrow. Even if the patient has a genital herpes, he needs to be treated. Usually, genital herpes will take time (5,7, or 10 days) depending on the infection and its sight. We will tell the patient this drug only will *shorten the duration of his symptoms* by 2 days. This the bottom line of the treatment. So, if my patient has a recurrent genital herpes, the herpes treatment is only going to benefit by 1 or 2 days.

- What I really need you to know:  
“**Oral acyclovir is only modestly beneficial in recurrent herpes labialis.**”  
In oral labialis you really have to use the balance of risk and benefit. 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 5 days (whether 2 times valacyclovir/day, or 4 times acyclovir/day), and that drug is going only to reduce the ulcer in your mouth by 1 day (this is what modestly means), then depending on the patient himself to take the drug or not. Telling him the only benefit of oral acyclovir is reduction by 1 day of symptoms.
- What about topical acyclovir? Is it really useful in the treatment of labialis?  
“Topical acyclovir cream is substantially less effective 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.

## Acyclovir adverse effects

- “Acyclovir common adverse drug reaction are nausea, vomiting, diarrhea, and headache”  
Headache is happening between 1-3% of the patients, that is making a problem of acyclovir; that’s why you have to balance between the risk and benefit when prescribing the drug. Generally speaking it is a **safe drug** that does NOT cause bone marrow suppression, which was the old problem of antiviral drugs.

- We are facing a problem when acyclovir is administered intravenously in the treatment of herpes encephalitis, that problem is simplified by **renal insufficiency and neurological toxicity**.

Renal insufficiency can be reduced by hydrating the patient. What is the idea behind that?

“Renal insufficiency, however, is uncommon with adequate hydration and avoidance of rapid infusion rate.”

What does this mean?

It means the cause of toxicity is the precipitation of acyclovir in kidney, to reduce precipitation, I should hydrate (force the patient to urinate), reducing the toxicity of the drug. This is a useful science that you should learn for all drugs that cause side-effects through precipitation.

## Docosanol

Another drug for herpes labialis. It is a topical (10 % cream) available without prescription.

“When applied within 12 hours of the onset of prodromal symptoms, five times daily, median healing time was shortened by 18 hours compared with placebo in recurrent orolabial herpes.”

This means that the drug is **not really efficient**.

## Ganciclovir

- **Cytomegalovirus (CMV)**, a severe virus, that can cause **bad pneumonia, retinitis, colitis.**

Whenever you see these symptoms with this virus, it is going to be treated with ganciclovir, a very close brother to the acyclovir.

The problem is that **ganciclovir produces bone marrow suppression**, while acyclovir does not. That is why we started our lecture saying that acyclovir is a golden drug of treatment.

Both acyclovir and ganciclovir are activated through viral thymidine synthase. However, clinic approved the opposite of that. We do not know the reason behind that. As we were trying ganciclovir we found a common, bad and old antiviral adverse effect of 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.

Pneumonia and colitis that are caused by CMV are very bad. As for retinitis (happens in the eyes) there's a topical application of ganciclovir in the form of **eye drops**.

Cytomegalovirus of special importance in AIDS patients, the virus usually happens with immunocompromised patients so we use ganciclovir.

Sometimes, patient with CMV infection, is not responding after being heavily treated ganciclovir, Why?

These patients are naïve patients who are infected with **resistant viruses**, so we have to change the strategy, from antimetabolite drugs (mimicking the nucleoside, phosphorylating it and then incorporating it into the DNA thus inhibiting the elongation of the DNA) to a direct DNA polymerase inhibitor by foscarnet.

## Foscarnet

- 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 problem with HIV is its integrase activity}
- the drug is active against Herpes (I, II, Varicella, CMV) including those resistant to acyclovir and ganciclovir.

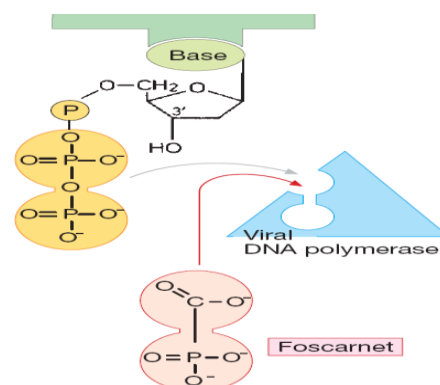
What does this mean?

- (1) It can be used instead of ganciclovir to treat CMV retinitis and other CMV infections
- (2) It can be used to treat H. simplex resistant to Acyclovir.

Is the drug approved as a safe drug ?

absolutely NO, nephrotoxicity is a common side effect (25%)

Look at the picture to the right, foscarnet will go to the viral DNA polymerase, get in the pocket and inhibit it directly.



## Vidarabine

It is an old drug that is not used anymore. We use it only in a case of vaccinia {used in preparing vaccines because it's weak} (vaccinia keratitis and in keratoconjunctivitis).

## Infuenza A&B

we treat influenza with four drugs

1. Oseltamivir
2. Zanamivir
3. Rimantadine
4. Amantadine

- Rimantadine and Amantadine are not used anymore, so forget about them. They have lost their susceptibility thus their approval. All (H1N1 viruses) are resistant to those drugs.
- We use two drugs called oseltamivir and zanamivir. Oseltamivir, is the *TAMI Flu*, you heard a lot about it when there was swine flu. Zanamivir, its trade name is *RELENZA*, it is coming to have the best place as a little resistant to *TAMI Flu (Oseltamivir)* began to arise.

What is the difference between them?

They are exactly the same. Both are inhibitors of **viral neuraminidase**. Viral neuraminidase catalyzes the cleavage of sialic acid and glycoproteins. If you stop this cut, you will stop the spread of the virus.

Simply, zanamivir, is administered by inhalation;  
while oseltamivir, is administered orally.

