بسم الله الرحمن الرحيم

FINAL | Lecture 5 Antiviral Drugs for Skin

VDO

ARMACOL

اللهم استعملنا ولا تستبدلنا

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Quiz on the previous lecture!



"رَبَّنَا ءَاتِنَا مِن لَّدُنكَ رَحْمَةُ وَهَيِّي لَنَا مِنْ أَمْرِنَا رَشَدًا"

REMEMBER FROM GENERAL PHARMACOLOGY

- Prodrug: An inactive compound that undergoes metabolic conversion in the body to release the active drug, improving its bioavailability, targeting, or tolerability slide 8.
- Bioavailability: is the fraction of an administered dose that reaches systemic circulation unchanged and becomes available to exert its pharmacological effect slide 14.

Antiviral Drugs for treatment of

HERPES SIMPLEX VIRUS (HSV) VARICELLA ZOSTER VIRUS (VZV) INFECTIONS

Alia Shatanawi



Patterns of Viral Infection

Check a quick comparison in the next slide ©

- Each of these are characterized by a different interaction between the virus and the host immune system

Acute infection (most common):

- <u>Complete viral clearance mediated by immune response</u>. → the virus won't stay in our body.
- E.g. Influenza, Rubella.

Latent infection:

- Initially Acute infection but followed by virus persistence in non-infectious form. → doesn't leave the body rather it stays in the body as dormant.
- Periodic reactivation of infection with viral shedding. (no active replicate but can reactivate at any time with existence of some triggers or conditions (weakening of immune system, stress, ...) → reactivating → shedding → symptoms)
- E.g. 1- Chickenpox: can remain latent in the body and later reactivate in the form of shingles (herpes zoster).
 2- Herpes simplex: remains dormant in the body and can reactivate intermittently, causing herpes labialis (cold sores) or genital herpes.

Chronic infection (progressive or persistent):

- Acute infection followed by lack of viral clearance \rightarrow stays in the body and replicates continuously or it stays in the tissue.
- Virus continuously shed or present in tissues and cause symptoms or progressive damage of organs (long term health complications.
- e.g. HIV, Hepatitis C.

Patterns of Viral Infection - Con.

	Acute infection	Latent infection	Chronic infection
Clearence	YES	NO	NO
Replicating continuously	NO	NO	YES
Reactivating	NO	YES	NO
Examples	Influenza, Rubella	Chickenpox, Herpes simplex	HIV, Hepatitis C

Both latent and Chronic infections start as acute infection, the difference is that:

- Chronic infection: symptoms and replicating of the virus persist longer.
- Latent infection: express virus persistence in non-infectious form followed by periodic reactivation of infection with viral shedding.

HSV and VZV infections

Oral nucleoside analogs licensed

- 1. Acyclovir
- 2. Valacyclovir
- 3. famciclovir.

All are well tolerated = good safety profile with minimal adverse effects on most of the cases.

- Acyclovir: was licensed first and is the only one of the three that is available for intravenous use in the United States, used for more severe or complicated infections; such as infections in immunocompromised patients or in cases of disseminated Herpes infection or in pateints who can't tolerate or can't take it orally^{* 1A}.

Comparative trials have demonstrated similar efficacies of these three agents for the treatment of HSV but modest superiority of famciclovir and valacyclovir for the treatment of herpes zoster infections with less frequent dosing compared to Acyclovir (Easier to adhere to(.

Nucleoside Analogs

- Mechanism of action (Interfere with the viral replication by:

- **Result in** "False" DNA building blocks or nucleosides (a nucleoside consists of a nucleobase and the sugar deoxyribose).
- Structural modification of nucleosides \rightarrow abnormal nucleosides \rightarrow nucleosides are no longer proper as DNA component \rightarrow disruption of viral DNA synthesis.
- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues
- Acyclovir.
- Valacyclovir(a pro-drug -needs to be activated in the body- with better availability)
- Foscarnet

Acyclovir

- Acyclovir is an acyclic guanosine derivative with clinical activity against HSV-1, HSV-2, and VZV,
- 10 times more potent against HSV-1 and HSV-2 than against VZV.
- In vitro activity against Epstein-Barr virus (EBV), cytomegalovirus (CMV), and human herpesvirus-6 (HHV-6) is present but weaker.

• How are these drugs activated?

Acyclovir

- Acyclovir requires three phosphorylation steps for activation (More clarification in the next slide(.
- It is converted first to the monophosphate derivative by the virus specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes → allow the drug to be incorporated into the viral DNA
- Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates— only in infected cells.
- Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:
- 1. competition with deoxy GTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex;
- 2. and chain termination following incorporation into the viral DNA.

Acyclovir

• A Guanine analogue with activity against Herpes viruses.

Acyclovir	AcycloGMP	AcycloGTP
Thy (ບ	midine kinase iral kinase)	Cellular kinases
After activation Acyclovir can work in two mechanisms:	 Selectively inhibits vir Incorporated into DNA 	al DNA polymerase. A and terminates synthesis
	Resistance: 1. ↓ activity of thymidir kinase 2. Altered DNA polymera	ie ase

Acyclovir activation & action





FIGURE 49–3 Mechanism of action of antiherpes agents.

Pharmacokinetics



- The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food.
- An intravenous formulation is available check slide 7 (*1A).
- Topical formulations (Direct application) produce <u>high local concentrations</u> in herpetic lesions, but systemic concentrations are undetectable by this route.
- Acyclovir is cleared primarily <u>by glomerular filtration and tubular secretion</u>. The half-life is 2.5–3 hours in patients with normal renal function → short half-life = quickly elimination of it → multiple doses of the drug administered for the patient whether oral or IV formulation.

• This slide compares the effectiveness of oral acyclovir in treating recurrent herpes labialis versus varicella infection.

Clinical Use

• Oral acyclovir is only modestly beneficial in recurrent herpes labialis (cold sores).

This is maybe because the virus can have a predictable course. While acyclovir can shorten the duration and reduce the number of outbreak, its effects are limited compared to other treatment options for HSV.

- In contrast, acyclovir therapy significantly decreases the total number of lesions, duration of symptoms, and viral shedding in patients with varicella (chickenpox).
- However, because VZV is less susceptible to acyclovir than HSV, higher doses are required.

Due to the variation in effectiveness, we need to tailor the antiviral therapy based on: the type of infection, the virus involved and the patient's condition.

This is the first part of the table. (Go to slide 26 for the second part).

Focus on the different uses

The Dr. mentioned all the uses

during the lecture.

No need to memorize the doses.

- Just notice the differences between the doses for the different drugs.

TABLE 49–1 Agents to treat or prevent herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections.

	Route of Administration	Use	Recommended Adult Dosage and Regimen	
Acyclovir ¹	Oral	* First episode genital herpes treatment	400 mg tid or 200 mg 5 times daily \times 7–10 days	
		* Recurrent genital herpes treatment	400 mg tid or 200 mg 5 times daily or 800 mg bid × 3–5 days or 800 mg tid × 2 days	• Also, notice that th
		Genital herpes in the HIV-infected * host treatment	400 mg 3–5 times daily × 5–10 days	half-life of this drug
	can lead to	 Genital herpes suppression in the HIV-infected host 	400-800 mg bid-tid	short, so it has to b administered multir
		* Herpes proctitis treatment	400 mg 5 times daily until healed	times a dau.
		* Orolabial herpes treatment	400 mg 5 times daily × 5 days	tintee a dagi
		* Varicella treatment (age ≥ 2 years)	800 mg qid × 5 days	•This can be a
Intraver		* Zoster treatment	800 mg 5 times daily × 7–10 days	drawback because multiple dosing will lower the adherence the patient to take proper doses of the
	Intravenous	* Severe HSV treatment	5 mg/kg q8h × 7–10 days	
		* Mucocutaneous herpes in the immunocompromised host treatment	10 mg/kg q8h × 7–14 days	
		* Herpes encephalitis treatment	10–15 mg/kg q8h × 14–21 days	
		* Neonatal HSV infection treatment	10–20 mg/kg q8h × 14–21 days	
		Varicella or zoster in the immunosuppressed * host treatment	10 mg/kg q8h × 7 days	drug.

Adverse effects:

Side effects of *acyclovir* treatment depend on the route of administration. For example, local irritation may occur from topical application

Oral Administration: headache, diarrhea, nausea, and vomiting

Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug intravenously.

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Resistance

• Mechanisms of resistance:

1- Altered or deficient thymidine kinase (the enzyme that's needed for the first phosphorylation for the activation of these nucleotide analogues)

2-Altered (mutated) **or deficient DNA polymerases** (Which can hinder the binding between the drug and the DNA polymerase; Thus less inhibition of the DNA polymerase).

- Have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients.
- Cross resistance to the other agents in this family occurs.

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Valacyclovir

- Valacyclovir is the L-valyl ester of acyclovir.
- It is rapidly converted to acyclovir after oral administration via first pass enzymatic hydrolysis in the liver and intestine, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir.

Clinical uses

- Approved uses of valacyclovir include treatment of:
- 1. first or recurrent genital herpes
- 2. suppression of frequently recurring genital herpes
- 3. orolabial herpes
- 4. treatment for varicella and herpes zoster
 - The low dose increases the patient's compliance.
- Once-daily dosing of valacyclovir for chronic suppression in persons with recurrent genital herpes has been shown to markedly decrease the risk of sexual transmission

Foscarnet

- Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or ٠ pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or cellular) kinases.
- Uses: CMV (retinitis and other CMV infections), Herpes simplex, and HIV. ٠

Main use/recommendation:-

Important!

Approved for CMV retinitis in immunocompromised hosts and for acyclovir-• resistant HSV infections.

Like HIV patients

Foscarnet

"فَنَادَىٰ فِي ٱلظُّلُمَٰتِ أَن لَّا إِلَٰهَ إِلَّا أَنتَ سُبَحْنَكَ إِنِّي كُنتُ مِنَ ٱلظَّالِمِينَ"

Mechanism of action:

- Works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis.
 → So it's a competitive inhibitor of these DNA polymerases.
- Mutation of the polymerase structure is responsible for resistant viruses.
- *Foscarnet* is poorly absorbed orally and must be injected intravenously.
- It must also be given frequently to avoid relapse when plasma levels fall (Fall below the minimum effective concentration).
- It is dispersed throughout the body, and greater than 10% enters the bone matrix, from which it slowly leaves.
- The parent drug is eliminated by glomerular filtration and tubular secretion.

Foscarnet

Adverse effects :

- Nephrotoxicity (25%) is the most common side effect
- Less common: anemia, nausea, and fever
- Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen.
- In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported

Vidarabine

Mechanism of action:

- Selectively inhibits virally induced DNA polymerase more than the endogenous enzyme.
- Vidarabine is a chain terminator and is active against herpes simplex, varicella zoster, and vaccinia.
- Use is limited to topical treatment of severe herpes simplex infection.
- Before the introduction of acyclovir, it was used in the treatment of herpes simplex encephalitis.
- Used in treatment of immunocompromised patients with herpetic and vaccinia keratitis and in keratoconjunctivitis.



Ganciclovir

 Same mechanism of action of Acyclovir, requires activation by triphosphorylation before inhibiting viral DNA polymerase causing termination of viral DNA elongation.

- Active against all Herpes viruses including CMV (100 times than acyclovir)
- Low oral bioavailability so, usually given I.V.
- Gel formulation is available for herpetic keratitis.



This drug has a Blackbox warning!

- Most common adverse effects: bone marrow suppression (leukopenia 40%, thrombocytopenia 20%), and CNS effects (headache, behavioral, psychosis, coma, convulsions).
- It's also a potential human carcinogen, mutagen (can lead to mutations that increase risk of cancer) and teratogen (contraindicated in pregnancy).
- Because of those effects, 1/3rd of patients have to stop treatment because of adverse effects.
- Drug of choice for CMV infections: retinitis, pneumonia, colitis. Important!

Continuation of	Famciclovir ¹	Oral	First episode genital herpes treatment	500 mg tid × 5–10 days
the table in slide			Recurrent genital herpes treatment	1000 mg bid × 1 day
15.			Genital herpes in the HIV-infected host treatment	500 mg bid × 5–10 days
The Dr. Mentioned all the uses during the			Genital herpes suppression	250 mg bid
			Genital herpes suppression in the HIV-infected host	500 mg bid
lecture.			Orolabial herpes treatment	1500 mg once
			Orolabial or genital herpes suppression	250-500 mg bid
			Zoster	500 mg tid × 7 days
	Valacyclovir ¹	Oral	First episode genital herpes treatment	1000 mg bid × 10 days
			Recurrent genital herpes treatment	500 mg bid × 3 days
			Genital herpes in the HIV-infected host treatment	500–1000 mg bid × 5–10 days
			Genital herpes suppression	500–1000 mg once daily
			Genital herpes suppression in the HIV-infected host	500 mg bid
			Orolabial herpes	2000 mg bid × 1 day
			Varicella (age ≥ 12 years)	20 mg/d tid × 5 days (maximum, 1 g tid)
			Zoster	1 g tid × 7 days
	Foscarnet ¹	Intravenous	Acyclovir-resistant HSV and VZV infections	40 mg/kg q8h until healed
	Docosanol	Topical (10% cream)	Recurrent herpes labialis	Thin film covering lesion q2h × 4 days
	Penciclovir	Topical (1% cream)	Herpes labialis or herpes genitalis	Thin film covering lesions q2h × 4 days
	Trifluridine	Topical (1% solution)	Acyclovir-resistant HSV infection	Thin film covering lesion 5 times daily until healed

¹Dosage must be reduced in patients with renal insufficiency.

HSV, herpes simplex virus; VZV, varicella-zoster virus.



For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

Reference Used:

رسالة من الفريق العلمي:

صبحانَ الله، والحمدُ لله، لا إله إلا الله، والله أكبر

