MSS

Pharmacology

LEC no. 9

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Nonsteroidal Anti-inflammatory Drugs (NSAIDs) and Analgesics

Dr. Alia Shatanawi

Naproxen and Ibuprofen

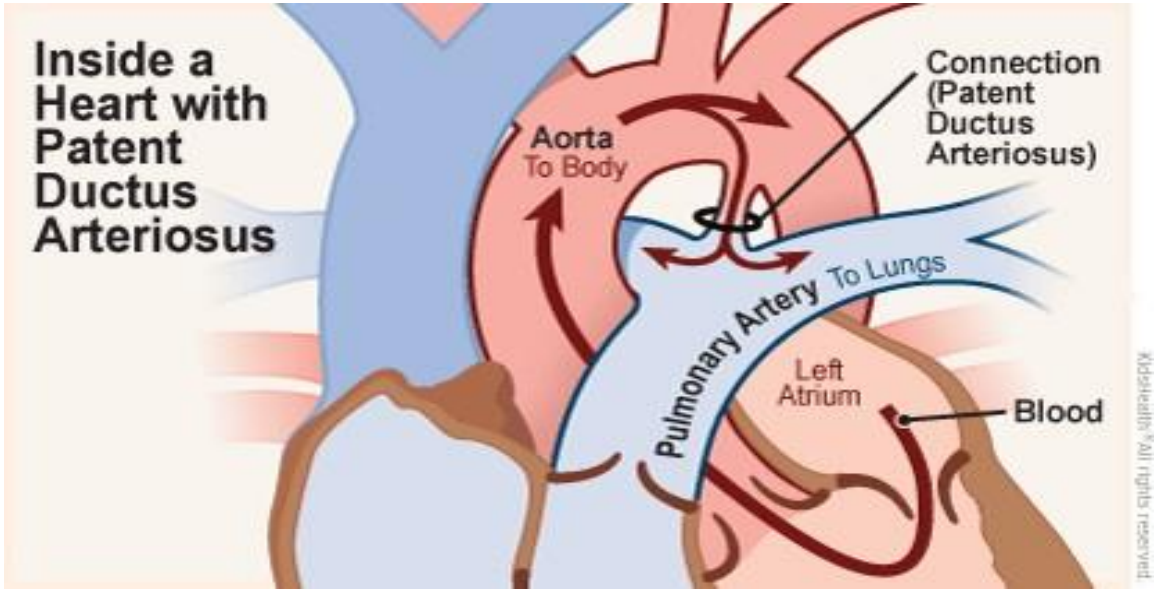
- Pregnancy : category C, category D 3rd trimester
- Increase the risk of cardiovascular thrombotic event, MI and stroke.
- Increase risk of GI bleeding.
- Ibuprofen not exceed 3200mg/day., and take with food or with water to avoid GI effect.

Doses aren't required for the exam

Acetic acid derivatives

indomethacin

- Despite its potency as an anti-inflammatory agent, the **toxicity** of **indomethacin** limits its use to the treatment of acute gouty arthritis, ankylosing spondylitis.



NSAIDS specially **indomethacin and Ibuprofen** has a role in closing PDA (patent ductus Arteriosus) by blocking the production of prostaglandins which have vasodilatory* effect ,details in the next slide.

What could happen if a mother takes indomethacin or ibuprofen (NSAIDS) in her last trimester of pregnancy (**contraindication**)? (side effect) this could cause an early closure of ductus arteriosus causing complications in fetus.

In general, indomethacin is more toxic than other NSAIDS, however, it is used topically as eye drops for inflammatory conditions of the eye

What is ductus Arteriosus?

The ductus arteriosus is a blood vessel in the fetal heart that connects the pulmonary artery to the aorta. It is a crucial part of **fetal circulation**, allowing blood to bypass the lungs, which are not functional in the womb, and receive oxygen from the mother's blood via the placenta.

What is PDA?

Shortly **after birth**, the ductus arteriosus usually closes, redirecting blood flow through the lungs for oxygenation as the baby begins to breathe independently. When the ductus arteriosus fails to close after birth, it's referred to as a patent ductus arteriosus (PDA), This can cause abnormal blood flow and may require medical intervention to correct.

What is the role of prostaglandins?

In fetuses, prostaglandins help keep the ductus arteriosus open, allowing blood to bypass the lungs and receive oxygen from the mother's blood via the placenta. This is important for fetal circulation. Prostaglandins help keep the ductus arteriosus open shortly after birth.

What is the role of NSAIDS specially **(indomethacin and Ibuprofen)**?

can help close a patent ductus arteriosus by blocking the production of prostaglandins. By inhibiting prostaglandin synthesis, NSAIDs promote closure of the ductus arteriosus, allowing it to function as it should after birth.

Oxicam derivatives

Piroxicam *and* ***meloxicam***

- *are used to treat RA, ankylosing spondylitis, and* osteoarthritis .
- They have **long half-lives**, which permit once-daily administration, and the parent drug as well as its metabolites are renally excreted in the urine.
- ***Meloxicam*** *inhibits both COX-1 and COX-2, with preferential binding for COX-2,* and at low to moderate doses shows less GI irritation than *piroxicam* .

You should know that all are anti Anti inflammatory except:
paracetamol

Which of the following is Cox 2 selective inhibitor?
A. Meloxicam
B. Celecoxib

Answer: Celecoxib

Diclofenac sodium

- Used PO 50mg after food, I.M. inj 75mg
- Diclofenac potassium is prompt release and has quicker onset where as the Diclofenac sodium is delayed release.
- Toxicity similar to others

Additional info.
In pharmacology, 'prompt release' signifies the rapid availability of a medication's active ingredients in the bloodstream after administration for swift therapeutic effects."

Acetaminophen

Paracetamol = Acetaminophen

. Acetaminophen inhibits prostaglandin synthesis in the **CNS** .

- This explains its **antipyretic and analgesic** properties .
- Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its **weak anti-inflammatory** activity .
- Acetaminophen does **not affect platelet** function or increase blood clotting time.

Therapeutic uses

It is an alternative drug for Patients who cant use aspirin / NSAIDs
It is safe for children with viral infection , pregnant women , peptic ulceration patients, patients with GI disease.

- Acetaminophen is a suitable **substitute** for the analgesic and antipyretic effects of aspirin for those patients with **gastric** complaints, those in whom prolongation of **bleeding** time would be a disadvantage, or those who do not require the anti-inflammatory action of aspirin.

- Acetaminophen is the analgesic/antipyretic of **choice** for **children** with viral infections or chickenpox (recall that aspirin increases the risk of **Reye's** syndrome .)

Adverse effects

- With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects .
- Renal tubular necrosis and hypoglycemic coma are rare complications of prolonged, large-dose therapy.
- **large doses Hepatic** necrosis, a very serious and potentially life-threatening condition can result.
- Renal tubular necrosis may also occur but lesser than NSAIDs.
- Periodic monitoring of liver enzymes tests is recommended for those on **high-dose acetaminophen.**

Paracetamol = Acetaminophen

- Weak PG synthesis inhibitor
- CNS actions: Paracetamol also modulates the endogenous cannabinoid system
- **Not**:
  - **antiinflammatory**
  - **Platelets inhibitor**
  - **Ulcerogenic** .....doesn't cause peptic ulcer
  - **Teratogenic** .....category A or B

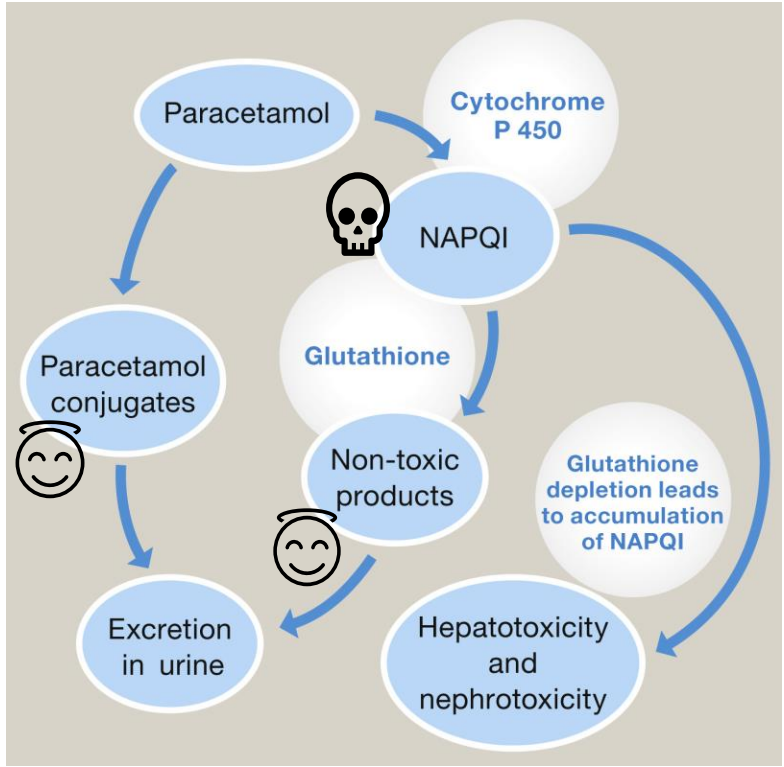
Pharmacokinetics

- Acetaminophen is rapidly **absorbed** from the GI tract. A significant first-pass metabolism occurs in the **luminal** cells of the intestine and in the **hepatocytes**.

- under **normal** circumstances, acetaminophen is conjugated in the **liver** to form inactive metabolites.

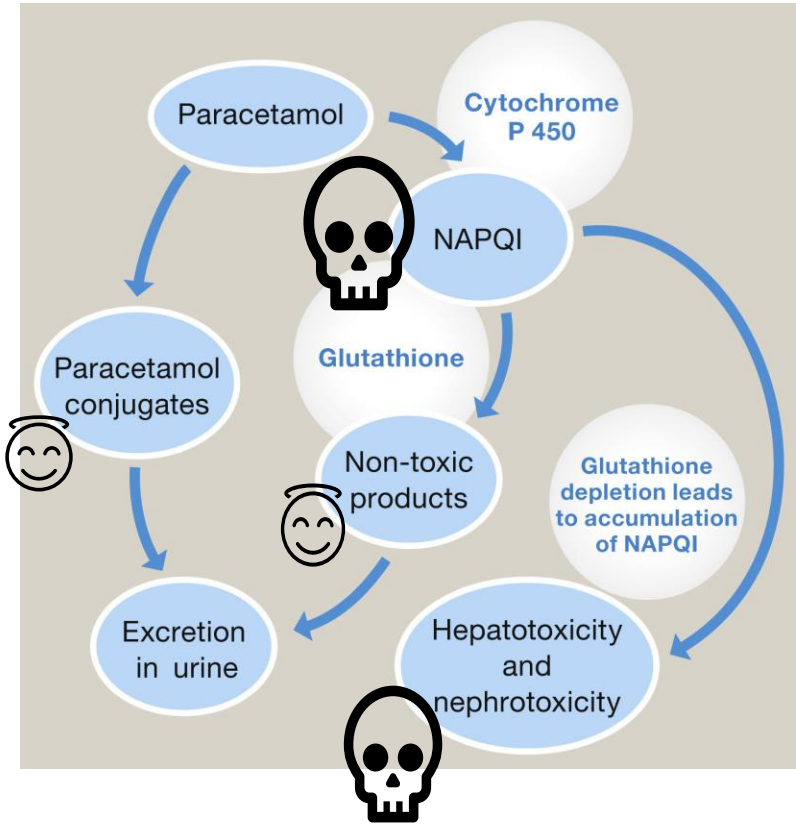
- A portion of acetaminophen is hydroxylated to form **N- acetylbenzoiminoquinone** a highly reactive with DNA , Proteins and potentially dangerous metabolite.

Additional figure



However, our body has a mechanism to get rid of this toxic metabolite which glutathione reduction system that reduces acetylbenzoiminoquinone by removing the extra electron.

Additional figure



- At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of **glutathione**, forming a nontoxic substance
- Acetaminophen and its metabolites are excreted in the urine.

When there is a high dose there will not be enough enzymes to deal with this toxic metabolites so it accumulates leading to DNA and hepatocytes damage causing liver necrosis

Paracetamol

- **Toxicity**
  - **Severe hepatotoxicity with high doses**

What is the way to get rid of that ??
Answer

  - **N- acetylcysteine is the antidote when given in the first 24hours.**
  - **بعد اربع و عشرين ساعة فات الاوان**

Additional info.

- N- acetylcysteine provides cysteine, a precursor to glutathione, which helps restore glutathione levels. By increasing glutathione availability, NAC enhances the detoxification of NAPQI.
- Additionally, NAC has antioxidant properties that directly scavenge free radicals,

Cyclooxygenase II Inhibitors: Celocoxib

- Inhibit prostaglandin synthesis by the COX-2 isozyme induced at sites of inflammation without affecting the action of the constitutively active “housekeeping” COX-1 isozyme found in the GI tract, kidneys, and platelets.

- COX-2 is constitutively active within the kidney, recommended doses of COX-2 inhibitors cause renal toxicities similar to those associated with traditional NSAIDs

- Clinical data have suggested a higher incidence of cardiovascular thrombotic events associated with COX-2 inhibitors such as rofecoxib and valdecoxib, resulting in their withdrawal from the market.

Celecoxib

- a selective COX-2 inhibitor—about 10–20 times **more** selective for COX-2 than for COX-.1

Remember that there is no pure selectivity,
increasing the does of the drug ---> losing the selectivity

- Drug interaction:
  It interacts occasionally with **warfarin**—as would be expected of a drug metabolized via CYP2C9

Warfarin مميع للدم
تصرف من دون وصفة له تفاعلات مع الكثير من الادوية الشائعة التي

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Drugs	Mechanism of action	Side effect	Other notes
Salicylate • *Aspirin*	• Irreversibly inhibits Cyclooxygenase 1 (COX-1) and COX-2 • Inhibition of COX-2 suppresses prostanoid synthesis providing analgesic, anti-pyretic and anti-inflammatory effects • Aspirin is weakly selective to COX-1	• **Gastrointestinal:** Inhibition of COX-1 causes dyspepsia and if severe gastric bleeding and ulceration • **Rashes:** Morbiliform rash, urticaria, toxic epidermal necrolysis (TEN) • **Acute renal failure** • **Increase blood pressure** • **Reduce effect of anti-hypertensives** (except CCB) • Salicylate poisoning in aspirin overdose (hyperventilation, tinnitus, deafness, vasodilatation)	• Contraindicated in active peptic ulceration, bleeding disorders, children under 16 years (risk of Reye's syndrome), severe cardiac failure
Propionate • *Ibuprofen* • *Naproxen*	• Competitive inhibitors of COX-1 and COX-2 • Both ibuprofen and naproxen are weakly selective to COX-1		• Contraindicated in GI bleed, ulceration, heart failure
Coxibs • *Celecoxib* • *Etoricoxib*	• Competitive inhibitor of COX-2 only at therapeutic dose	• Similar to other NSAIDs • Less gastrointestinal side-effects	• Contraindicated in active GI bleed, ulceration, cerebrovascular disease, inflammatory bowel disease, ischemic heart disease, heart failure, peripheral arterial disease • Monitor blood pressure
Paracetamol	• Exact mechanism unknown but has ability to inhibit COX pathways • Good analgesic and anti-pyretic but poor anti-inflammatory effects	• Paracetamol overdose can cause liver damage • Presents with nausea and vomiting, associated with right subcostal pain and tenderness	

GRAM PROJECT

Notes:

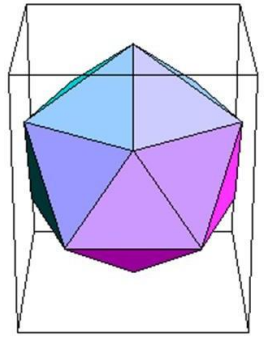
- **Slides are enough for the exam.** 👌
- **Doses are not required.**
- **We will focus on MOA, Clinical use, Contradictions, Side effects & steps of activation.**

Antiviral Drugs for treatment of

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

Alia Shatanawi

MOAs of Antivirals in general:
Prevent viruses' attachment to the cell , entry, replication and do inhibition for transcriptase, also it prevents assembly or the release of the virions.



Patterns of Viral Infection

1. Acute infection:

- Complete viral clearance mediated by immune response
- All the symptoms resolve after the infection is gone.
- E.g. Influenza, Rubella.

2. Latent infection :

- Acute infection but followed by virus persistence in non- infectious form.
- Periodic reactivation of infection with viral shedding.
- The Infection gets reactivated ; when we have exam after couple days 😐, stress, immunosuppression , temperature changes (sudden cold or hot weather) and hormonal changes.
- E.g. Chickenpox, Herpes simplex (cold sore, small ulcers) الحمو ، البرد

3. Chronic infection (progressive or persistent):

- Acute infection followed by lack of viral clearance
- Virus continuously shed or present in tissues
- e.g. HIV, Hepatitis C

HSV (Herpes simples) and VZV (varicella zoster) infections

Oral nucleoside analogs licensed

1. Acyclovir (prototype الجد الأكبر)
2. Valacyclovir
3. famciclovir.

All are well tolerated .

Acyclovir was licensed first and is the only one of the three that is available for intravenous use in the United States .

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

Nucleoside Analogs

- MOA:
- **Result in** "False" DNA building blocks **or nucleosides**(a nucleoside consists of a nucleobase and the sugar deoxyribose .)
- This abnormal nucleoside undergoes bio-activation by attachment of three phosphate residues

- **Acyclovir.**
- **Valacyclovir(a pro-drug with better availability)**
- **.Foscarnet**

1. 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.

Acyclovir

- Acyclovir is a prodrug needs activation to function.
- Acyclovir requires three phosphorylation steps for activation .

- It is converted first to the monophosphate derivative by the virus specified thymidine kinase (gives specificity) and then to the di- and triphosphate compounds by host cell enzymes.

- Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates— only in infected cells .it doesn't cause any damages on none infected cells.

- Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms :

1. competition with deoxyGTP 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.

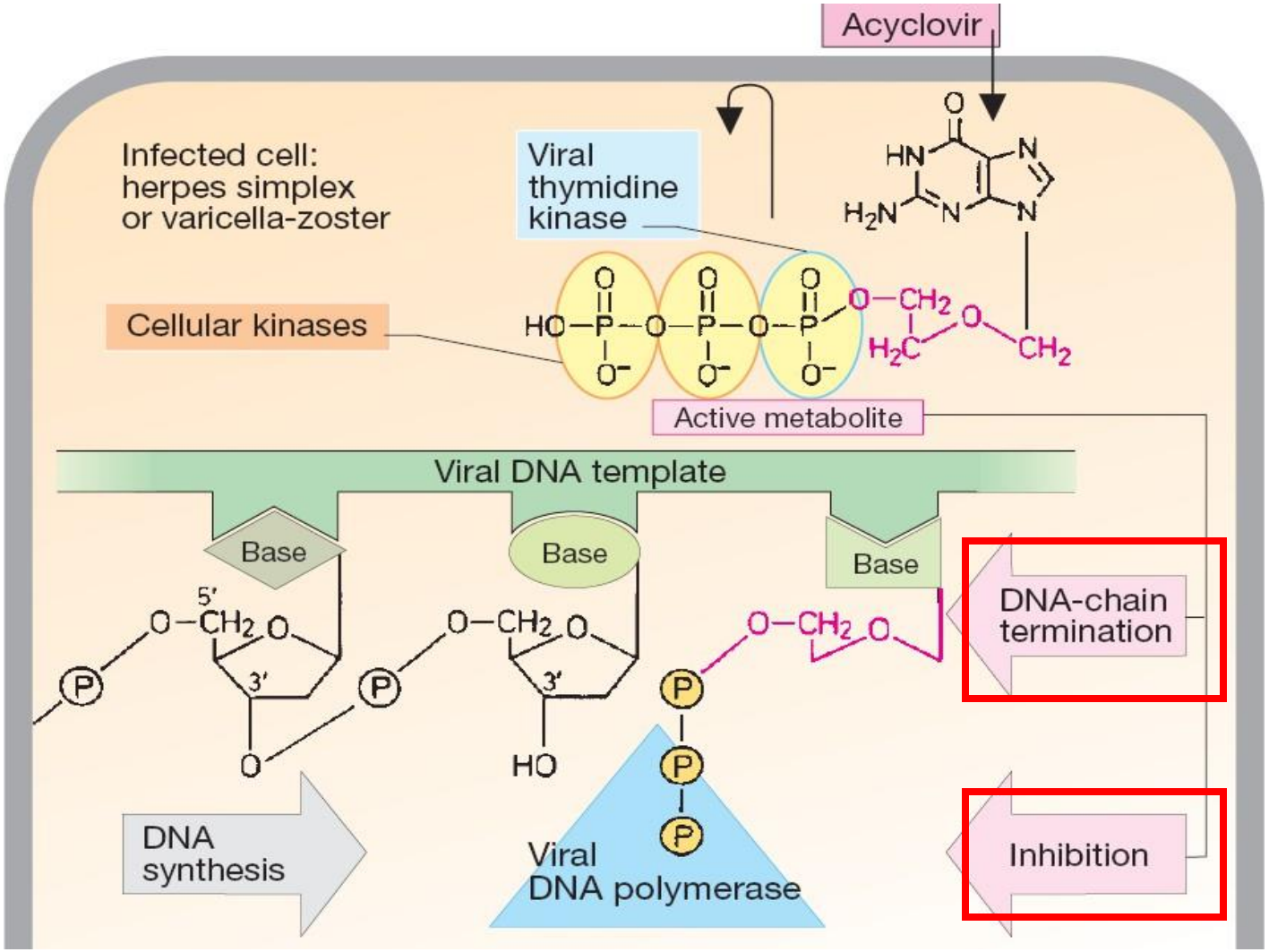
Acyclovir

A Guanine analogue with activity against Herpes viruses.

1. Selectively inhibits viral DNA polymerase.
2. Incorporated into DNA and terminates synthesis

Resistance:

1. activity of thymidine kinase ↓
2. Altered DNA polymerase


Acyclovir
Infected cell:
herpes simplex
or varicella-zoster
Viral
thymidine
kinase
Cellular kinases
Active metabolite
Viral DNA template
Base
Base
Base
DNA-chain
termination
DNA
synthesis
Viral
DNA polymerase
Inhibition

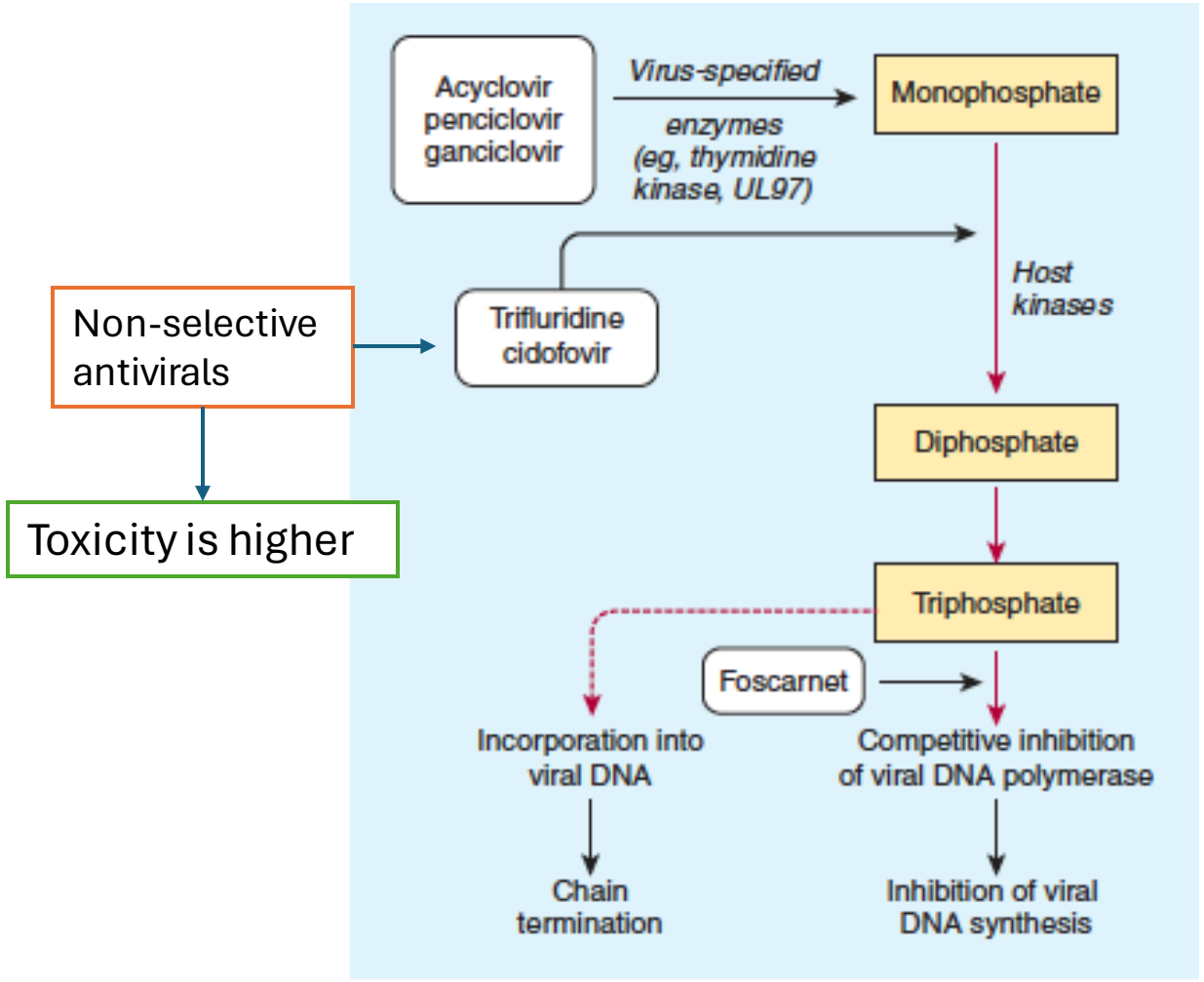


FIGURE 49–3 Mechanism of action of antiherpes agents.

Pharmacokinetics

- The bioavailability of oral acyclovir is low (15–20%) and is unaffected by food .
- An intravenous formulation is available.
- Topical formulations produce high concentrations in herpetic lesions & shingles, but systemic concentrations are undetectable by this route.
- Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is 2.5–3 hours in patients with normal renal function

Read only

Clinical Use

- Oral acyclovir is only modestly beneficial in recurrent herpes labialis .
- In contrast, acyclovir therapy significantly decreases the total number of lesions, duration of symptoms, and viral shedding in patients with varicella .
- However, because VZV is less susceptible to acyclovir than HSV, higher doses are required.

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 × 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
		Genital herpes in the HIV-infected host treatment	400 mg 3–5 times daily × 5–10 days
		Genital herpes suppression in the HIV-infected host	400–800 mg bid–tid
		Herpes proctitis treatment	400 mg 5 times daily until healed
		Orolabial herpes treatment	400 mg 5 times daily × 5 days
		Varicella treatment (age ≥ 2 years)	800 mg qid × 5 days
		Zoster treatment	800 mg 5 times daily × 7–10 days
	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
	Topical (5% cream)	Herpes labialis treatment	Thin film covering lesion 5 times daily × 4 days

Genital herpes, HIV

Immunocompromised (mainly), systematically (affect other organs).

Topical lesions (mild), shingles (oral + topical administration)

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.

Resistance

Altered or deficient thymidine kinase and DNA polymerases 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.

2. 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

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

Understand

3. Foscarnet

Unlike most antiviral agents, *foscarnet* [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or cellular) kinases .

- **Uses**: CMV **cytomegalovirus** (retinitis and other CMV infections), Herpes simplex, and HIV.

approved for CMV retinitis in:

1. **immunocompromised hosts and**
2. **for *acyclovir*-resistant HSV infections .**

Foscarnet

works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis .
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 .
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.by kidneys

Foscarnet

Adverse effects:

- Nephrotoxicity (25%) is the most common side effect. IMPORTANT!!
- anemia, nausea, and fever

Due to chelation with divalent cations, hypocalcemia ↓Ca^{+2} and hypomagnesemia ↓Mg^{+2} are also seen.
In addition, hypokalemia ↓K^{+1} , hypo- and hyperphosphatemia, seizures, and arrhythmias عدم انتظام ضربات القلب have been reported

4. Vidarabine

- **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.**

5. 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.**

Ganciclovir

- Most common adverse effects: bone marrow suppression (leukopenia 40%, thrombocytopenia 20%), and CNS effects (headache, behavioral, psychosis, coma, convulsions). Special side effects!!

- 1/3rd of patients have to stop treatment because of adverse effects.

- Drug of choice for CMV infections: retinitis, pneumonia, colitis . Expected question 🤔

Read only

Famciclovir[1]	Oral	First episode genital herpes treatment	500 mg tid × 5–10 days
		Recurrent genital herpes treatment	1000 mg bid × 1 day
		Genital herpes in the HIV-infected host treatment	500 mg bid × 5–10 days
		Genital herpes suppression	250 mg bid
		Genital herpes suppression in the HIV-infected host	500 mg bid
		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

[1]Dosage must be reduced in patients with renal insufficiency.

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

اللهم إنا نشكو إليك أطفالاً قُصفت ومزقت، ونساءاً اغتصبت وقُتلت، وشيوخاً أُهينت واعتقلت، وشباباً تحت جنازير الدبابات فُرمت، وأكباداً جُوعت، وصغاراً وكباراً من الشراب والطعام حُرمت !!
اللهم فرج كربنا، ونفس همنا، وتولى أمرنا، وأطفئ نار حربنا !!