Antiviral Agents

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- **DNA Viruses**
  - HSV
  - VZV
  - CMV
  - EBV
  - HBV
  - Adenoviruses
  - Papillomaviruses
  - Polyomaviruses(BK,JC)

- **RNA Viruses**
  - Influenza
  - Parainfluenza
  - RSV
  - Measles
  - Enterovirus
  - Adenovirus
  - HCV
  - Ebola virus

Antiviral agents can be categorized as:

- Virucidals
- Antiviral chemotherapeutic
- Immunomodulators

Virucidal agents inactivate the virus on contact and include detergents, solvents, and ultraviolet light.

These agents are not useful for treatment because healthy tissue also is destroy.

Immunomodulators (immune globulin, monoclonal antibody, interferons,…)

manipulate the immune system to enhance its ability to contain viral infection.

Antiviral chemotherapeutic agents usually inhibit virus specific events :

adsorption or attachment to the host cell

(pleconaril)

penetration and uncoating of the viral genome

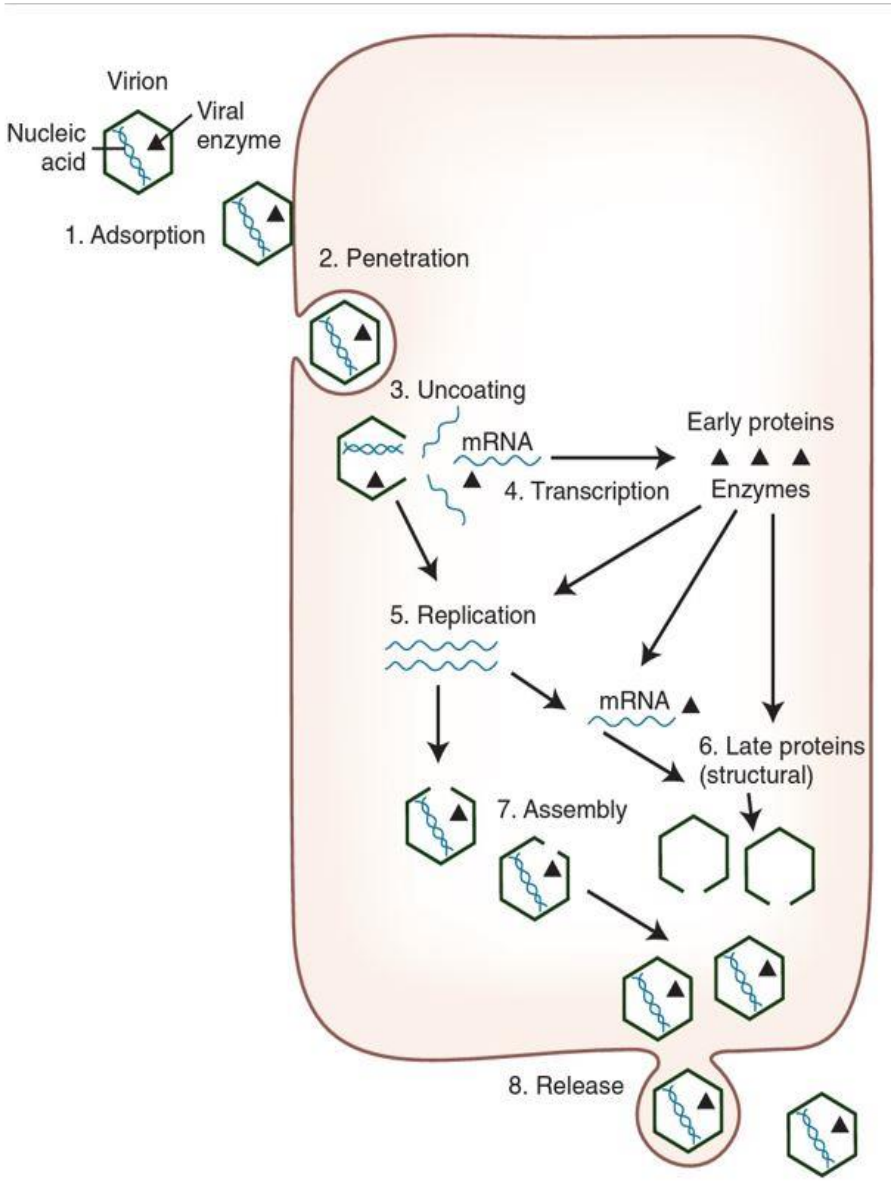
(amantadine)

viral gene expression and nucleic acid synthesis

(acyclovir, ganciclovir)

viral assembly of virions, infectious viral particles

(interferons)



Antiviral agents

- Antiviral agents usually have a narrow range of activity.
- As a general rule, antiviral agents are specific to certain families of viruses.
- The anti herpesvirus drugs do not work against influenza, the anti-hepatitis C drugs do not work against HBV, and so on.

Antiviral agents

- Most anti viral agents are administered as single therapeutic agents.
- Double and triple combination therapy is also important for treatment in IC hosts or where presence or emergence of drug resistant viruses is likely.

Antiviral agents active against RNA viruses

- Amantadine — Influenza A
- Rimantadine — Influenza A
- *Oseltamivir* — *Influenza A & B*
- Zanamivir — Influenza A & B
- Ribavirin — RSV & Hepatitis C

Oseltamivir

- **Mechanism :**

  Neuraminidase inhibitor

Neuraminidase permits influenza virus to penetrate through the mucoproteins present in respiratory secretions to the surfaces of cells, and inhibition of this enzyme prevents viral access and infection of cells

Resistance :

Mutations that induce amino acid changes in viral neuroaminidase alter enzyme stability or activity

Mutations in hemagglutinin produce a reduced affinity for cell receptors

Mutations in both produce resistant influenza viruses

Pharmacokinetics Oseltamivir

- Oseltamivir has good oral bioavailability.
- Approximately **75% to 80%** of the administered dose is absorbed.
- Peak plasma concentration are reached within 3 to 4 hours but may be delayed , **but not reduced** , if the drug is given with food.
- Dosage should be adjusted for patients with renal insufficiency or renal failure.
- Adjusment in liver failure is unclear from the available evidence.

Oseltamivir dosage

- Oseltamivir is administered orally
- Available in 75 mg capsules and in suspension (30 mg/5ml,12mg/ml).
- The usual adult dosage :

  75 mg twice daily for treatment

- The pediatric dose :

  preterm : 1mg/kg/dose bid

  infant ≤ 8 mo: 3 mg/kg/dose bid

  infant ≥ 9mo: 3.5 mg/kg/dose bid

  children and adolessents:

  ≤ 15 kg : 30 mg bid

  16-23 : 45 mg bid

  24-40: 60 mg bid

  > 40: 75 mg bid

Adverse effect

- Nausea and vomiting , which may be lessened by administration of the drug with food
- Psychosis and other psychiatric disorders(rarely)
- Renal ,metabolic and cardiac reactions such as bradycardia and QT prolongation

Antiviral agents active against DNA viruses

- **Acyclovir** **HSV,VZV**
- **Valacyclovir** **HSV,VZV, Zoster**
- Penciclovir HSV, mucocutaneous
- Famciclovir HSV, VZV, zoster
- **Ganciclovir** **CMV**
- **Valganciclovir** **CMV**
- **Foscarnet** **CMV**
- Cidofovir CMV

Acyclovir

Spectrum of activity

- It has selective activity against the herpes family of viruses.
- It has the **most potent antiviral activity** against HSV type 1.
- Inhibitory concentrations of HSV2 and VZV are also high.
- EBV replication is inhibited by acyclovir at a mean concentration.

Acyclovir (pharmacokinetics)

- Acyclovir is available for topical, oral and IV administration.
- Systemic absorption of acyclovir after topical application to intact skin is minimal (< 0.01 µg/ml)
- **The bioavailability of oral acyclovir is low (15-20%)**
- Most of the administered dose of acyclovir is excreted unchanged in urine.
- Dose adjustment ,according to creatinine clearance is needed in renal failure.
- **Probenecid** administration decreases renal clearance and prolongs the half –life .
- Acyclovir is distributed widely into a variety of body fluid:

  saliva (13% of plasma level), vaginal secretions(15-170%),

  zoster vesicular fluid(90-100%), breast milk(>300%), CSF(50%).

More than half the drugs is removed by hemodialysis, but very little is removed after peritoneal dialysis.

- **Oral acyclovir** significantly reduces viral shedding, clinical symptoms, and time until lesion healing in normal and IC with variety of **mucocutaneous lesions** (orolabial, pharyngeal, genital, rectal, gingivostomatitis, whitlow, skin, dendritic corneal ulcer) in primary HSV infection.

- Administration of oral acyclovir to children with gingivostomatitis is appropriate and can be expected to modify the duration of symptoms if it is initiated early in the clinical course.

- **IV acyclovir** is used to treat all sever or life-threatening diseases caused by HSV and VZV, including:

encephalitis, hepatitis, neonatal disease, acute retinal necrosis syndrome, mucocutaneous, and zoster , with or without visceral dissemination , in both normal and immunocompromised patients.

- **Topical acyclovir** may decrease healing time and viral shedding slightly in mucocutaneous lesions of patients with **primary infection with HSV**.
- **Topical therapy** also may produce a **mild clinical benefit** in immunocompromised patients with zoster lesions.

Oral acyclovir is formulated as 200-mg,400mg,800 mg tablets, and 200 mg/5 ml suspension.

Mucocutaneous lesions:

- Primary infection with HSV

  In adult and adolescents (*200 mg administered five times daily for 10 days*)

  The usual pediatric oral dose (15 mg/kg/dose (max 200 mg) daily for 10 days)

- Recurrent HSV disease in adult and adolescents :

  800 mg three times daily for 2 days, 400 mg three times daily for 5 days,

  200 mg five times daily for 5 days.

Acyclovir dosage

- HSV, mucocutaneous: 5% ointment 6-7 days
  15 mg/kg/dose po 5 days
  (max 200 mg/dose)
  5-10 mg /kg/dose IV q 8h
- HSV, encephalitis: 10-15 mg/kg/dose IV q8h
- HSV, neonatal: 20 mg/kg/dose IV q8h
- HSV, chickenpox and zoster : **20 mg/kg/dose Po q 6h**
  (max 800 mg)
  10-20 mg/kg/dose IV q 8 h
  (500 mg /m2/dose)

Adverse effects

- Topical : pain, local irritation, usually caused by the polyethylene glycol base.

  Hand washing must be performed after each local application to avoid autoinoculation or person –to- person transmission.

- Oral : nausea, vomiting, rash, or headache.

  neutropenia in 46% of infants (long term)

Extravasation of drug (PH 9-11) : inflammation, ulceration, necrosis of surrounding tissue

Neurotoxicity occurs rarely (renal insufficiency)

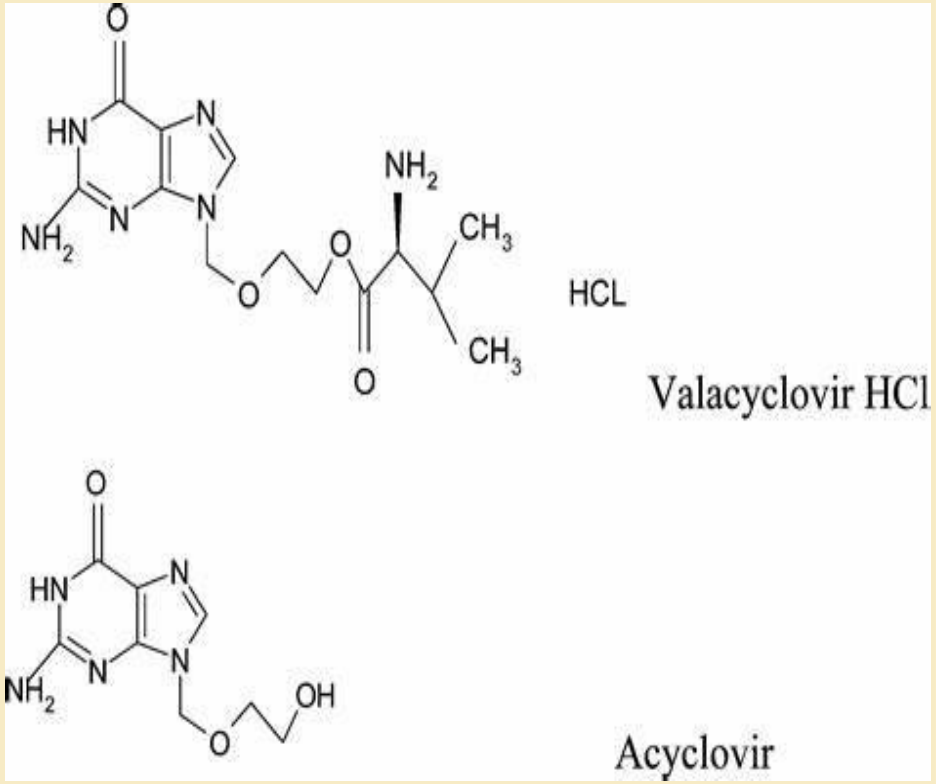
Renal tubular damage, crystalline nephropathy, interstitial nephritis (5%)

(hydration, infusion time of 1 hour, keeping urine-specific gravidity 1.010)

Is safe in pregnancy , especially during the last trimester, does not appear any significant adverse effect.

valacyclovir

- The valine ester prodrug of acyclovir.
- Is converted rapidly to acyclovir.
- The same selective spectrum of antiviral activity against the herpesviruses as acyclovir does.
- Has the same mechanisms of action and resistant.



Valacyclovir (pharmacokinetics)

- After oral administration, valacyclovir is absorbed rapidly from GI tract.
- It is metabolized by first pass through the intestinal tract and also by liver into acyclovir and L-valine.
- **54% bioavailability (vs. 20% for acyclovir), which is not altered by food**.
- The half time is prolonged in patients with renal insufficiency.
- The drug is removed by hemodialysis.
- No dosage adjustment necessary in hepatic impairment.

Valacyclovir(clinical indication)

- In treatment of **primary and recurrent mucocutaneous** disease caused by **HSV-1, HSV2, and VZV.**
- Is available only in 500-mg,1000mg tablet.
- In primary genital herpes : 1 gr twice daily for 10 days.
- In recurrent genital herpes: 3-5 days
- A daily dose of 500 mg has been used safely for longer than a year to suppress recurrences of HSV disease.
- VZV: 1 gr three times a day for at least 7 days

60 mg /kg /day in pediatrics

Ganciclovir

Mechanism of action:

Ganciclovir is phosphorylated by viral and cellular kinases into ganciclovir triphosphate which competitively inhibits the binding of deoxyguanosine triphosphate to DNA polymerase resulting in inhibition of viral DNA synthesis.

This antiviral compound has selective activity against the herpesviruses, with uniquely **potent antiviral** activity against CMV.

Inhibits HSV-1, HSV-2,VZV, CMV, EBV, HHV-6, HHV-7, HHV-8.

It has in vitro activity activity against adenoviruses and HBV well.

Ganciclovir

- Patients may be infected with single or multiple strains of CMV, with both drug-sensitive and drug-resistant strains mixed in the population or in different body compartments.

- Ganciclovir resistance has been detected in 8% to 38% of IC patients who have received prolonged administration.

Pharmacokinetics

- After IV administration, ganciclovir is distributed in CSF at 24% to 70% of plasma levels, and 38% of plasma levels enter brain tissue.
- Drug levels in a aqueous, vitreous, and sub retinal fluid in the eye are comparable to serum levels and even higher levels can be achieved with intravitreal.
- Accumulates in breast milk in animal models.
- The plasma half –life is 2 to 4 hours in adult with normal renal function , and longer than 24 hours in renal insufficiency.
- Hydration will enhance elimination of the drug, and hemodialysis removes 60% of ganciclovir in plasma.

Clinical indication

- Treatment of stablished CMV disease; for early or preemptive therapy in IC patients.
- For prophylaxis of high- risk patients (CMV seropositive / have received TX from CMV-seropositive donors.
- Ganciclovir prophylaxis is also effective in preventing HSV infection in IC patients.
- In newborns congenitally infected with CMV.

Dosage

- The recommended dose for induction therapy for serious CMV disease : 5 mg/kg/dose every 12 hours for 2-3 weeks.
- Maintenance therapy doses : 5mg/kg/dose every 12 to 24 hours.
- Newborns with moderate to sever congenital CMV:

  6mg/kg/dose every 12 hours

Adverse effect

- Local reaction: phlebitis, irritation, blistering, ulceration at or around the infusion site (alkaline PH=11).
- Systemic toxicity : reversible neutropenia, thrombocytopenia, CNS disturbance, nephrotoxicity, liver dysfunction.
- If the neutropenia is sever (ANC<500), ganciclovir should be halted temporarily until the neutrophil count recovers.
  - ganciclovir readministered, at the same or half the original dose.
  - some experts have used recombinant GCS-F .
- CNS disturbance: headache, behavioral changes, psychosis, seizure, and coma.
- Ganciclovir is also mutagenic, carcinogenic, and immunosuppressive.

Valganciclovir

- Valganciclovir is the L-valyl ester (prodrug) of ganciclovir.
- It is metabolized rapidly in the body to ganciclovir.
- Therefore has the same selective spectrum of activity as ganciclovir against herpesviruses, especially CMV, as well as limited activity against adenoviruses and HBV.

Mechanism of action

- It is metabolized rapidly in the body to ganciclovir.
- Ganciclovir is monophosphorylated by viral protein kinase(coded for by UL97 genes) in CMV-infected cells.
- Further phosphorylated to the active form ganciclovir triphosphate by cellular kinases.
- Viral DNA synthesis is inhibited by ganciclovir triphosphate.

Resistance

- Isolates of CMV become resistant by mutations in:

  UL97 genes, the viral kinase gene, or in UL54, the viral DNA polymerase gene.

  Mutations in UL97 confer resistance to ganciclovir and valganciclovir.

  Mutations in UL54 confer double or triple resistance to ganciclovir, foscarnet, and cidifovir.

Pharmacokinetics

- The bioavailability of valganciclovir is high, **approximately 60%(vs 6-9% for ganciclovir).**
- Absorption is **enhanced** significantly with the **ingestion of food**.
- The drug is excreted by the kidneys.
- Dosage: neonates and infants up to 6 months of age: 16 mg/kg/dose every 12 hours.
- For pediatric patients : 7x BSA xCrCl every 12 hours
- Maximum dose : 900 mg/dose
- Solution oral : 50 mg.ml
- **Tablet : 450 mg (valcyte**)
- Should be adjusted monthly for weight gain and also may be mixed with small amount of formula or breast milk.

Foscarnet

- Foscarnet is a pyrophosphate analogue that directly inhibits virus and cellular DNA polymerase.
- It also has activity against **HIV** and **HBV**.
- At concentration of 100 to 300 µmol/L, **CMV** is inhibited.
- Whereas slightly lower concentrations (80-200 µmol/L) inhibit **HSV type 1** and **2,VZV, EBV, and HHV-8**.
- Concentration between 20 and 200 µmol/L appear to inhibit HBV.

Foscarnet

- Foscarnet also inhibit most acyclovir- resistant HSV and VZV strains and most ganciclovir- resistant CMV strains.
- Combinations of ganciclovir and foscarnet are synergistic against CMV.
- Combinations of zidovudine and foscarnet appear to be synergistic against HIV.

Pharmacokinetics

- CSF levels are usually approximately 60% of plasma levels.
- Vitreous concentrations in the eye are the same as or slightly higher than plasma levels.
- **Oral has poor bioavailability(<10%).**
- The drug is eliminated by renal excretion.
- The drug is removed by hemodialysis, but not appreciably by peritoneal dialysis.

Dosage

- The usual dosage of foscarnet for induction therapy : 60 mg/kg/dose every 8 hours for 3 weeks.
- Maintenance therapy is 90 to 120 mg/kg per day.
- The dose should be given slowly, during the course of 2 hours (or no faster than 1 mg/kg/min), to reduce renal toxicity .
- Prehydration with saline with each dose are recommended to reduce renal toxicity.

Adverse effects

Foscarnet is associated with serious adverse effects.

- Renal toxicity with azotemia, proteinuria, crystaluria, renal tubular acidosis, or necrosis, and interstitial nephritis.
- Metabolic abnormality : hypocalcemia and hypercalcemia, hypophosphatemia, hyperphosphatemia, hypomagnesemia, hypokalemia.
- Symptoms of these acute metabolic abnormality include :

  perioral tingling, numbness or paresthesias of the limbs, seizure, tetany, and cardiac dysrhythmias.
- CNS side effects : headache, tremor, seizure, and behavioral changes.
- Abnormal liver function test

A. OVERVIEW OF NON-HIV, NON-HEPATITIS B OR C VIRAL PATHOGENS AND USUAL PATTERN OF SUSCEPTIBILITY TO ANTIVIRALS

Virus	Acyclovir	Baloxavir	Cidofovir	Famciclovir	Foscarnet	Ganciclovir
Cytomegalovirus			+		+	+
Herpes simplex virus	++			+	+	+
Influenza A and B viruses		+				
Varicella-zoster virus	++			+	+	+

Virus	Letermovir	Oseltamivir	Peramivir	Valacyclovir	Valganciclovir	Zanamivir
Cytomegalovirus	+				++	
Herpes simplex virus				++	+	
Influenza A and B viruses		++	+			+
Varicella-zoster virus				++		

NOTE: ++ = preferred; + = acceptable; ± = possibly effective (see text for further discussion); – = unlikely to be effective; [blank cell] = untested.

Remdesivir

- Remdesivir is a nucleotide prodrug of an adenosine analog. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.
- Remdesivir has demonstrated in vitro and in vivo activity against SARS-CoV-2.
- Intravenous remdesivir is approved by FDA for the treatment of COVID-19 in adults and pediatric patients aged ≥28 days and weighing ≥3 kg.

Clinical indication

- In non-hospitalized patients with mild to moderate COVID-19 who are at high risk of progressing to severe disease, remdesivir should be started within 7 days of symptom onset and administered for 3 days.
- Hospitalized patients should receive remdesivir for 5 days or until hospital discharge, whichever comes first.
- If a patient does not clinically improve, clinicians may extend the treatment course for up to 5 additional days (for a total duration of 10 days)

Dosage

- Adult and pediatric ≥ 12y and wt ≥ 40:

  single loading dose of 200 mg on day1

  maintenance doses of 100 mg qd for total 10 day

- Pediatric patients weighing 3.5 kg through <40 or <12 y:

  single loading dose of 5 mg/kg on day

  maintenance doses of 2.5 mg/kg for total 10 day

Adverse Effects

- Remdesivir can cause gastrointestinal symptoms (nausea), elevated transaminase levels, an increase in prothrombin time without a change in the international normalized ratio, and hypersensitivity reactions.
- Remdesivir may need to be discontinued if a patient's alanine transaminase (ALT) level increases to >10 times the upper limit of normal, and it should be discontinued if increases in ALT levels and signs or symptoms of liver inflammation are observed.
- It can be used without dose adjustment in patients with an estimated glomerular filtration rate (GFR) of <30 mL/min, including those receiving dialysis.

Adverse Effects

- Remdesivir should be administered in a setting where severe hypersensitivity reactions, such as anaphylaxis, can be managed.
- Sinus bradycardia have been reported (within 24 hours of first dose).
- Patients should be monitored during the infusion and observed for at least 1 hour after the infusion as clinically appropriate.

Thank you