Anti-herpes Drugs: Pharmacological Treatment for Herpes Infections

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In this article, we will study in detail various anti-herpes drugs, their mechanism of action, adverse effects/toxicity, contraindications, drug interactions, and drugs of choice. Other important pharmacological and therapeutic aspects of individual drugs will also be studied.

Overview of Herpes Infections

Herpes infections are very common; most adults have one or more herpes infections in their lifetime. Herpes infections are caused by **herpesviridae viruses**, a family of **DNA viruses**.

Herpes Simplex Infections

Although both **herpes simplex virus type 1 (HSV-1)** and **herpes simplex virus type 2 (HSV-2)** can cause orofacial and genital infections, HSV-1 more commonly causes the former and HSV-2 the latter.

Important points:

- HSV-1 predominantly causes infections of the **labial areas** (areas above the waist).

- HSV-2 predominantly causes infections in the **genital areas** (areas below the waist).

Clinical manifestations and the course of the infection depend on the patient's age and immunological status, ranging from asymptomatic subclinical infections to life-threatening infections in immunocompromised patients. Primary infections tend to be more severe, with systemic signs and symptoms, while repeated infections usually show isolated local involvement.

Pathogenesis of Herpes Infections

The mode of infection of HSV is through mucosal surfaces or through abraded skin. Sexual infections occur in the adult (vaginal, anal, orogenital and oroanal transmissions). In the neonate, perinatal infection is usually contracted during passage through the birth canal.

After entry into the host, the virus reaches the epidermis/dermis, where replication starts. The virus then reaches either the autonomic or sensory nerve endings. After reaching a sufficient replication number in the nerve endings, the virus is transported intra-axonally into the cell bodies.

The centripetal movement of the virus from the axon to the cell body and then spread to the mucocutaneous surface through peripheral nerve endings causes larger surface area involvement. New lesions may occur away from the site of inoculation, and the virus may be recovered from neurons far away from the site of inoculation.

HSV viremia is another chief mechanism for the extension of infection with HSV-2.

In the case of HSV-1, latent infection is most commonly observed in the trigeminal ganglia. While in HSV-2 infection, the sacral root ganglia (S2–S5) are most frequently affected.

Herpes Labialis

Clinical Spectrum of Herpes Infections

HSV infection may be a primary infection or an infection caused by reactivation of the virus:

1. Primary infection (the host acquires the infection for either type of HSV for the first time and lacks the antibodies in the serum)
2. Reactivation of HSV in affected neurons (latent)

Herpes Genitalis in Females

When compared to recurrent infection, the primary infection has a longer duration of symptoms because it involves both mucosal and extramucosal sites. The incubation period for both types of HSV infection is 6–8 days.

The spectrum of HSV infection includes the following conditions:

- Acute herpetic gingivostomatitis
- Acute herpetic pharyngotonsillitis
- Herpes labialis

- Genital herpes (primary, recurrent, and subclinical)
- Herpetic keratitis
- Encephalitis
- Neonatal herpes

Varicella-Zoster Infections

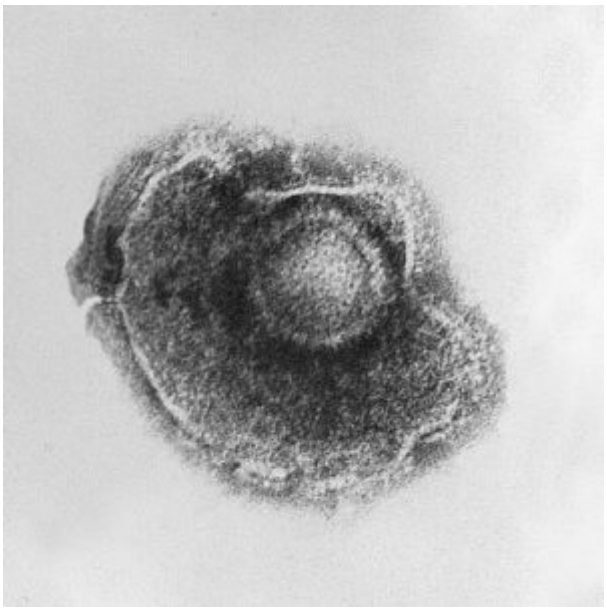

Image: “Electron micrograph of a Varicella (Chickenpox) Virus. Varicella or Chickenpox, is an infectious disease caused by the varicella-zoster virus, which results in a blister-like rash, itching, tiredness and fever.” by CDC/Dr. Erskine Palmer/B.G. Partin. License: Public Domain

Varicella-zoster virus (VZV) causes **chickenpox** following initial exposure to the virus, and reactivation of the virus later in life causes **herpes zoster (shingles).**

Chickenpox usually occurs in **childhood** and presents as a characteristic **rash** with a low-grade **fever**. In a healthy child, this infection is usually **self-limiting** and benign, but it can be more serious in adults and immunocompromised children; in these cases, different **prodromal symptoms**, such as **headaches**, nausea, and myalgia, are possible, as well as serious clinical manifestations sometimes leading to **death**.

The structure of the virus is similar to the herpes virus, with a lipid envelope**, icosahedral symmetry**, and **double-stranded DNA**.

Herpes zoster usually occurs many years after the primary infection, manifesting as a typical **vesicular rash** affecting only one or **two dermatomes** and accompanied by **pain**, tingling, and altered sensations or sensory loss in the affected area. A common sequela of herpes zoster is **post-herpetic neuralgia** (i.e., persistent pain along the distribution of the rash).

Antiviral Drugs

Acyclovir

Mechanism of Action

Acyclovir is activated as follows:

1. Virus-specific enzymes (e.g., **thymidine kinase**) convert **acyclovir** to **acyclovir monophosphate.**
2. **Host cell kinases** convert **acyclovir monophosphate** to **diphosphate** and then to **the triphosphate.**

Because virus-specific enzymes are required, acyclovir is activated only in infected cells. Some virus strains lack **thymidine kinase** and thus show resistance to acyclovir. In these cases, **cross-resistance** to famciclovir, ganciclovir, and valacyclovir also occurs.

Acyclovir triphosphate inhibits **viral DNA synthesis** via the following two mechanisms:

- It acts as a competitive substrate for **DNA polymerase**

It irreversibly binds to the viral DNA and causes **chain termination.**

Clinical uses

Acyclovir is used in the treatment of HSV-1, HSV-2, and VZV infections, even though it shows greater potency in the treatment of HSV than VZV. The order of sensitivity is HSV-1 > HSV-2 > VZV = EBV. Accordingly, higher doses are required when given for VZV.

There are three formulations of acyclovir available: oral, intravenous, and topical. Oral acyclovir is unaffected by food, but bioavailability is low (20%). Topical acyclovir can be useful in skin lesions and has the advantage of no systemic reactions. In HSV encephalitis, neonatal HSV infection, or other HSV and/or VZV infections in immunocompromised patients, intravenous acyclovir is a drug of choice.

Adverse effects/toxicity

Because the drug is activated only in infected cells, acyclovir is generally well tolerated. However, headache and gastrointestinal symptoms (nausea and diarrhea) have been observed. In some cases, intravenous administration can lead to acute renal toxicity (which is dose-dependent) and some neurological adverse effects, such as seizures and delirium. These adverse effects can be avoided by proper hydration of the patient during therapy.

Drug interactions

Because of the possibility of renal toxicity, concurrent use of acyclovir with other nephrotoxic agents should be avoided. Cimetidine and probenecid increase exposure to acyclovir through decreased clearance of the drug. In patients receiving concomitant zidovudine, lethargy and somnolence are possible effects.

Contraindications

The use of acyclovir is contraindicated in those with previous allergic reactions to acyclovir or penciclovir. Kidney disease and massive volume loss are relative contraindications for acyclovir therapy because of potential kidney damage.

Valacyclovir

Mechanism of action

Valacyclovir is metabolized by first-pass metabolism into acyclovir. Oral valacyclovir has much better bioavailability than oral acyclovir.

Clinical uses

Genital herpes, herpes labialis, and VZV infections. Valacyclovir is available only as an oral formulation.

Adverse effects/toxicity

Valacyclovir has almost the same metabolism as acyclovir, making it a safe medication. In high doses, symptoms like confusion, seizures, and hallucinations have been reported, but are rare. Gastrointestinal intolerance, thrombotic thrombocytopenic purpura, and hemolytic uremic syndrome are possible, but extremely rare.

Contraindications

Previous allergic reactions to acyclovir or penciclovir

Famciclovir

Mechanism of action

Famciclovir is a prodrug that is metabolized to penciclovir through first-pass metabolism (deacetylation and oxidation).

Mnemonics

It is phosphorylated by virus-specific thymidine kinase, making this drug very specific, similar to acyclovir; it is a competitive inhibitor of DNA polymerase, but it does not cause chain termination. Penciclovir triphosphate does not have the affinity to a DNA polymerase that the acyclovir triphosphate has, but it reaches a higher concentration in the cells.

Clinical uses

Genital herpes, herpes labialis, and herpes zoster. Only available as an oral formulation.

Adverse effects/toxicity

Headaches and gastrointestinal symptoms

Drug interactions

Famciclovir should not be administered 24 hours before or 14 days after VZV immunization.

Contraindications

Known hypersensitivity

Penciclovir

Penciclovir is an active metabolite of famciclovir, and it is available only as a topical agent. It is used in genital and labial herpes. There are no interactions and adverse effects are rare except for application site reactions (pruritus, mild pain, and transient burning) that occur in 1% of patients.

Docosanol

Docosanol inhibits viral entry into cells by preventing fusion between the viral envelope and the plasma membrane. It is used in the treatment of herpes labialis and is available only as a topical agent. Application site reactions occur in 2% of patients.

Trifluridine

Mechanism of action: Trifluridine (C) inhibits DNA synthesis in HSV-1, HSV-2, CMV, vaccinia, and several adenoviruses. Similar to other abovementioned nucleoside analogs, it is phosphorylated intracellularly and then inhibits DNA synthesis by competitively inhibiting viral DNA polymerase. Trifluridine is not selective for infected cells, making it inadequate for systemic use.

Clinical uses

Trifluridine (topical application only) is used in the treatment of HSV-1-associated or HSV-2-associated keratoconjunctivitis and epithelial keratitis.

Cutaneous application of trifluridine, alone or in combination with interferon alfa, is effective in acyclovir-resistant HSV infections.

Adverse effects/toxicity

Some palpebral edema and burning sensation happen in 1%–10% of patients.

Drug interactions

No interactions.

Contraindications

Previous allergic reactions.

Ganciclovir

Mechanism of action: Similar to other abovementioned nucleoside analogs, ganciclovir is activated intracellularly by the virus-specific enzyme phosphotransferase UL97 and then inhibits DNA synthesis by competitively inhibiting viral DNA polymerase.

Clinical uses: Ganciclovir is mainly used in the treatment of CMV infections, and it is 100 times more potent against CMV than acyclovir.

There are three formulations available: oral, intravenous, and an ocular implant.

When administered orally, ganciclovir has poor bioavailability, but oral administration is less likely to cause myelosuppression than IV administration.

In HIV patients, IV ganciclovir is used to delay the progression of CMV retinitis, and its effectiveness is increased when combined with foscarnet. IV administration is also recommended in immunocompromised patients suffering from CMV esophagitis, colitis, and pneumonitis.

Ocular implants are used in the treatment of CMV retinitis and must be surgically replaced every 5–8 months.

Adverse effects/toxicity

Myelosuppression is the most common adverse effect of ganciclovir, and it is usually associated with intravenous administration. Adverse effects like headache, gastrointestinal symptoms, rash, and peripheral neuropathy are also observed. Very rarely, toxicity of the liver and central nervous system may occur.

Drug interactions

Myelosuppression is more likely with concomitant administration of azathioprine, mycophenolate mofetil, or zidovudine. Probenecid and trimethoprim increase serum ganciclovir levels and ganciclovir increases serum didanosine levels.

Contraindications

Previous allergic reactions to acyclovir or ganciclovir, severe thrombocytopenia, and neutropenia.

Valganciclovir

Valganciclovir is metabolized to ganciclovir in the liver and intestinal wall. The only formulation available is oral, and its bioavailability is better than that of ganciclovir. It is used for the treatment of CMV retinitis and the prevention of CMV infections in transplant patients. Because valganciclovir is metabolized to ganciclovir, all of the adverse effects, interactions, and contraindications are the same as those for ganciclovir.

Foscarnet

Mechanism of action

Foscarnet (phosphonoformic acid) inhibits DNA polymerase of herpesviruses, as well as RNA polymerase and reverse transcriptase of HIV. It does not need to be phosphorylated in order to be active. In the aforementioned enzymes, foscarnet blocks the pyrophosphate binding site; this results in the inhibition of pyrophosphate cleavage from deoxynucleotide triphosphates. Lack of or defects in enzymes such as thymidine kinase do not confer resistance to foscarnet.

Clinical uses

CMV infections and acyclovir-resistant HSV and VZV infections. Because of its poor bioavailability when administered orally, the only formulation available is intravenous.

Adverse effects/toxicity

Renal impairment and electrolyte disturbances—hypocalcemia, hypercalcemia, hypophosphatemia, hyperphosphatemia, hypokalemia, and hypomagnesemia. The speed of administration has to be closely monitored and adjusted based on creatinine clearance. Genital ulcerations can occur because of the ionized drug present in the urine. Other adverse effects include gastrointestinal symptoms, liver toxicity, anemia, fatigue, and central nervous system toxicity (headache, hallucinations, and seizures).

Drug interactions

Anemia is more likely to appear in patients receiving concomitant zidovudine, while central nervous system toxicity happens more often in patients being treated with concomitant imipenem.

Contraindications

Previous allergic reactions to foscarnet. Use in patients with previous renal impairment or in those receiving nephrotoxic drugs, such as amphotericin B, should be closely monitored.

Cidofovir

Mechanism of action

Cidofovir does not require viral enzymes for phosphorylation to its active diphosphate, thus making it effective against the strains of CMV and HSV with or without a defective thymidine kinase. Cidofovir is an inhibitor of viral DNA polymerase, but it also acts as its alternative substrate, causing inhibition of DNA synthesis.

Clinical uses

An intravenous preparation is used in the treatment of CMV retinitis.

Adverse effects/toxicity

The most common adverse effect is proximal tubular nephrotoxicity. Each cidofovir infusion must be titrated based on creatinine clearance and the presence of protein in the urine, and the patient must be hydrated during the administration of the medication. Ocular toxicity (uveitis, ocular hypotony) and neutropenia are possible.

Drug interactions

Concomitant administration of nephrotoxic drugs (such as amphotericin B and aminoglycosides) should be avoided. Probenecid causes increased adverse effects and drug interactions.

Contraindications

Known hypersensitivity. Because of the possibility of severe renal toxicity, patients with previous renal impairment should not receive cidofovir.

Idoxuridine

Idoxuridine is a thymidine analog. Because it competes with thymidine, it gets inserted in the DNA, causing it to break. It is used for the treatment of HSV keratitis and genital and labial herpes. Only topical formulations (eye drops) are available. It is rarely used because acyclovir is safer and more effective.

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Notes