Chapter-12

Antiviral Drugs

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ABSTRACT

Antiviral drugs are medications designed to treat viral infections by inhibiting the replication and spread of viruses within the host organism. Unlike antibiotics, which target bacteria, antiviral drugs are specifically tailored to interfere with viral processes. These drugs work by targeting various stages of the viral life cycle, including viral entry, uncoating, replication, assembly, and release. Common antiviral drugs include acyclovir, which is used to treat herpes simplex virus infections, and oseltamivir, used for influenza. The development of antiretroviral therapy (ART) has significantly improved the management of HIV/AIDS, turning it into a manageable chronic condition. Antivirals such as remdesivir have also been pivotal in treating emerging viral infections like COVID-19. The challenge in antiviral drug development lies in the high mutation rates of viruses, which can lead to drug resistance. Therefore, combination therapies, which use multiple drugs with different mechanisms of action, are often employed to enhance efficacy and reduce the likelihood of resistance. The continued research and development of antiviral drugs are crucial in combating both existing and emerging viral threats, improving public health outcomes globally.

Introduction to Antiviral Drugs

Antiviral drugs are a class of medications specifically designed to treat viral infections by inhibiting the development and replication of viruses. Unlike bacteria, viruses are obligate intracellular parasites, meaning they require a host cell to replicate and propagate. This unique characteristic makes the development of antiviral drugs particularly challenging, as these medications must selectively target viral processes without causing significant harm to the host's cells. Antiviral therapy has been crucial in the management of various viral infections, including HIV/AIDS, hepatitis, influenza, and herpesvirus infections. With the rise of new and emerging viral diseases, the importance of effective antiviral treatments continues to grow.

Classification of Antiviral Drugs

Antiviral drugs can be classified based on their mechanism of action and the stage of the viral life cycle they target. The main classes include:

1. Nucleoside and Nucleotide Analogues
2. Non-Nucleoside Polymerase Inhibitors
3. Protease Inhibitors

4. Entry and Fusion Inhibitors
5. Integrase Inhibitors
6. Neuraminidase Inhibitors
7. Other Antiviral Agents

1. Nucleoside and Nucleotide Analogues

Examples: Acyclovir, Zidovudine (AZT), Lamivudine, Tenofovir

Mechanism of Action: These drugs mimic the natural nucleosides or nucleotides that are incorporated into viral DNA or RNA during replication. Once incorporated, they cause premature chain termination or introduce mutations, inhibiting viral replication.

2. Non-Nucleoside Polymerase Inhibitors

Examples: Efavirenz, Nevirapine

Mechanism of Action: These inhibitors bind directly to the viral RNA-dependent DNA polymerase (reverse transcriptase) or DNA-dependent RNA polymerase, causing conformational changes that inhibit the enzyme's activity without mimicking nucleosides.

3. Protease Inhibitors

Examples: Ritonavir, Saquinavir, Lopinavir

Mechanism of Action: Protease inhibitors target viral proteases, which are enzymes essential for the cleavage of viral polyprotein precursors into functional viral proteins. By inhibiting these proteases, the maturation of viral particles is disrupted.

4. Entry and Fusion Inhibitors

Examples: Enfuvirtide, Maraviroc

Mechanism of Action: These drugs prevent the virus from entering host cells by blocking the binding of the virus to the host cell receptors or inhibiting the fusion of the viral envelope with the host cell membrane.

5. Integrase Inhibitors

Examples: Raltegravir, Elvitegravir

Mechanism of Action: Integrase inhibitors block the viral enzyme integrase, which is required for the integration of viral DNA into the host genome, a critical step in the viral replication cycle.

6. Neuraminidase Inhibitors

Examples: Oseltamivir (Tamiflu), Zanamivir (Relenza)

Mechanism of Action: These drugs inhibit the viral enzyme neuraminidase, which is necessary for the release of new viral particles from infected cells. This inhibition prevents the spread of the virus to other cells.

7. Other Antiviral Agents

Examples: Interferons, Remdesivir

Mechanism of Action: Interferons are proteins that enhance the immune response against viral infections. Remdesivir, used for COVID-19, is a nucleoside analogue that inhibits viral RNA polymerase.

Pharmacology of Acyclovir

Chemical Structure: Acyclovir is a synthetic nucleoside analogue of guanine.

Mechanism of Action: Acyclovir is selectively activated by viral thymidine kinase, which phosphorylates acyclovir to acyclovir monophosphate. Cellular enzymes further convert it to acyclovir triphosphate, which is incorporated into viral DNA by viral DNA polymerase. This incorporation leads to premature chain termination, thereby inhibiting viral DNA synthesis and replication.

Pharmacokinetics

- **Absorption:** Oral bioavailability is relatively low (15-30%). Intravenous and topical formulations are also available.
- **Distribution:** Widely distributed in body fluids, including the cerebrospinal fluid (CSF). It crosses the placenta and is excreted in breast milk.
- **Metabolism:** Acyclovir is minimally metabolized.
- **Excretion:** Primarily excreted unchanged in the urine by glomerular filtration and tubular secretion. The half-life ranges from 2 to 3 hours in patients with normal renal function.

Therapeutic Uses

- Treatment of herpes simplex virus (HSV) infections, including genital herpes, herpes labialis, and HSV encephalitis.
- Treatment and prophylaxis of varicella-zoster virus (VZV) infections, including chickenpox and shingles.
- Prophylaxis in immunocompromised patients to prevent HSV and VZV infections.

Adverse Effects

- **Common:** Nausea, diarrhea, headache.
- **Severe:** Renal toxicity (crystalluria), neurotoxicity (tremors, confusion), particularly with intravenous administration.
- **Local:** Inflammation and phlebitis at the injection site with intravenous use.

Pharmacology of Famciclovir

Chemical Structure: Famciclovir is the diacetyl ester prodrug of penciclovir, a guanine analogue.

Mechanism of Action: Famciclovir is rapidly converted to penciclovir in the liver. Penciclovir, similar to acyclovir, is phosphorylated by viral thymidine kinase to penciclovir monophosphate and then to penciclovir triphosphate by cellular kinases. Penciclovir

triphosphate inhibits viral DNA polymerase, reducing viral DNA synthesis and replication without causing chain termination.

Pharmacokinetics

- **Absorption:** Famciclovir has good oral bioavailability (about 77%). It is rapidly absorbed and converted to penciclovir.
- **Distribution:** Penciclovir is widely distributed in tissues. It is also excreted in breast milk.
- **Metabolism:** Famciclovir is metabolized to penciclovir by first-pass metabolism in the liver.
- **Excretion:** Penciclovir is excreted unchanged in the urine. The half-life of penciclovir is about 2 to 3 hours.

Therapeutic Uses

- Treatment of acute herpes zoster (shingles).
- Treatment and suppression of recurrent genital herpes.
- Treatment of herpes labialis (cold sores).
- Prophylaxis and treatment of HSV infections in immunocompromised patients.

Adverse Effects

- **Common:** Headache, nausea, diarrhea.
- **Severe:** Rarely, acute renal failure, particularly in patients with pre-existing renal impairment.
- **Other:** Rash, pruritus, and other hypersensitivity reactions.

Pharmacology of Tenofovir

Chemical Structure: Tenofovir is an acyclic nucleoside phosphonate analogue of adenosine monophosphate.

Mechanism of Action: Tenofovir is converted intracellularly to tenofovir diphosphate, which acts as a competitive inhibitor of HIV-1 reverse transcriptase and HBV polymerase. By incorporating into the viral DNA chain, tenofovir causes premature termination of DNA elongation, thereby inhibiting viral replication.

Pharmacokinetics

- **Absorption:** Oral bioavailability is approximately 25-39% when taken on an empty stomach, and increases with a high-fat meal.
- **Distribution:** Widely distributed in the body, including into cerebrospinal fluid. It is also excreted in breast milk.
- **Metabolism:** Tenofovir is not extensively metabolized.
- **Excretion:** Primarily excreted unchanged in the urine via glomerular filtration and active tubular secretion. The half-life is approximately 17 hours.

Therapeutic Uses

- Treatment of HIV-1 infection in combination with other antiretroviral agents.
- Treatment of chronic hepatitis B virus (HBV) infection.

Adverse Effects

- **Common:** Nausea, vomiting, diarrhea, dizziness, rash.
- **Severe:** Renal toxicity (including acute renal failure and Fanconi syndrome), bone toxicity (osteomalacia and decreased bone mineral density).
- **Other:** Lactic acidosis and hepatomegaly with steatosis, particularly in patients with pre-existing liver disease.

Pharmacology of Zanamivir

Chemical Structure: Zanamivir is a neuraminidase inhibitor structurally related to sialic acid.

Mechanism of Action: Zanamivir inhibits the influenza virus neuraminidase enzyme, which is essential for the release of new viral particles from infected cells and for the virus's ability to spread. By blocking this enzyme, zanamivir prevents the virus from spreading in the respiratory tract, thereby limiting the infection.

Pharmacokinetics

- **Absorption:** Zanamivir is administered via inhalation, which results in direct delivery to the respiratory tract. Systemic absorption is low.
- **Distribution:** After inhalation, zanamivir is distributed in the respiratory tract, with minimal systemic exposure.
- **Metabolism:** Zanamivir is not metabolized.
- **Excretion:** Excreted unchanged in the urine. The half-life of zanamivir is approximately 2.5 to 5 hours.

Therapeutic Uses

- Treatment of acute, uncomplicated influenza A and B in patients who have been symptomatic for no more than 2 days.
- Prophylaxis of influenza A and B.

Adverse Effects

- **Common:** Cough, throat discomfort, nasal symptoms.
- **Severe:** Bronchospasm and decline in lung function, especially in patients with underlying respiratory diseases such as asthma or chronic obstructive pulmonary disease (COPD).
- **Other:** Rare cases of allergic reactions, including orofacial edema.

Zanamivir

1. **Mechanism of Action:** Zanamivir directly inhibits the neuraminidase enzyme on the surface of influenza viruses, similar to oseltamivir. By preventing the release of new viral particles, zanamivir helps to reduce the severity and duration of influenza symptoms.

2. **Administration:** Zanamivir is available in an inhaled form, typically delivered using a device called a Diskhaler. It is not well absorbed through the gastrointestinal tract, so it is administered via inhalation to achieve higher concentrations in the respiratory tract.

3. **Pharmacokinetics:** Zanamivir has poor oral bioavailability, and the majority of the inhaled dose is deposited in the respiratory tract. It has a relatively short half-life of approximately 2-5 hours and is primarily excreted unchanged in the urine.

Raltegravir

1. **Mechanism of Action:** Raltegravir inhibits the activity of the HIV integrase enzyme. HIV integrase is responsible for integrating the viral DNA into the host cell genome. By inhibiting this process, raltegravir prevents the replication of the virus within the host cell.

2. **Administration:** Raltegravir is administered orally, typically as raltegravir potassium. It is well-absorbed from the gastrointestinal tract, and its absorption is not significantly affected by food.

3. **Metabolism and Elimination:** Raltegravir undergoes glucuronidation in the liver, primarily by uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The metabolites are eliminated through both feces and urine.

4. **Pharmacokinetics:** The drug has a relatively short half-life, requiring twice-daily dosing in most cases.

Elvitegravir

1. **Mechanism of Action:** Elvitegravir also inhibits the integrase enzyme of HIV, preventing the integration of viral DNA into the host cell genome.

2. **Administration:** Elvitegravir is often co-formulated with other antiretroviral drugs in a fixed-dose combination. It is administered orally and is typically given with a boosting agent, cobicistat, to increase its bioavailability.

3. **Metabolism and Elimination:** Elvitegravir undergoes metabolism primarily by cytochrome P450 3A4 (CYP3A4) in the liver. Cobicistat, a pharmacokinetic enhancer, is used to inhibit CYP3A4 and increase the plasma concentrations of elvitegravir. The metabolites are eliminated through feces.

4. **Pharmacokinetics:** Elvitegravir has a longer half-life compared to raltegravir, allowing for once-daily dosing when used in combination with cobicistat.

Entecavir

1. **Mechanism of Action:** Entecavir is a guanosine nucleoside analogue. It is phosphorylated intracellularly to its active form, entecavir triphosphate. This active metabolite competes with the natural substrate deoxyguanosine triphosphate for incorporation into the growing viral DNA chain. Once incorporated, it causes premature termination of the chain, inhibiting the reverse transcription process and blocking HBV replication.

2. **Administration:** Entecavir is administered orally and is well-absorbed from the gastrointestinal tract.

3. **Metabolism and Elimination:** Entecavir is primarily eliminated unchanged in the urine through a combination of glomerular filtration and active tubular secretion. The drug has a relatively long half-life, allowing for once-daily dosing in most cases.

Telbivudine

1. **Mechanism of Action:** Telbivudine is a thymidine nucleoside analogue. Similar to entecavir, it undergoes phosphorylation to its active triphosphate form, which is incorporated into the growing viral DNA chain. This incorporation inhibits the reverse transcriptase enzyme, leading to chain termination and inhibition of HBV replication.

2. **Administration:** Telbivudine is administered orally, and it is well-absorbed from the gastrointestinal tract.

3. **Metabolism and Elimination:** Telbivudine is primarily eliminated unchanged in the urine. It does not undergo significant hepatic metabolism. The drug has a relatively long half-life, allowing for once-daily dosing.

Sofosbuvir

1. **Mechanism of Action:** Sofosbuvir is a nucleotide analog inhibitor of the hepatitis C virus (HCV) RNA polymerase. Once inside the liver cells, it is converted into its active form, which is a substrate for the NS5B polymerase. The active form is incorporated into the growing HCV RNA chain, leading to chain termination and inhibition of viral replication.

2. **Administration:** Sofosbuvir is administered orally and is typically used in combination with other antiviral medications to form a complete regimen for the treatment of hepatitis C.

3. **Metabolism and Elimination:** Sofosbuvir is metabolized in the liver to its active form. The active metabolite has a long half-life, allowing for once-daily dosing. It is excreted primarily through the urine.

Remdesivir

1. **Mechanism of Action:** Remdesivir is a broad-spectrum antiviral medication initially developed for Ebola virus infection. It is a nucleotide analog that inhibits the action of the viral RNA-dependent RNA polymerase. Remdesivir is thought to be incorporated into the

viral RNA chain during replication, leading to premature termination and inhibition of viral replication.

2. **Administration:** Remdesivir is administered intravenously and is typically used in a hospital setting for the treatment of severe cases of COVID-19.

3. **Metabolism and Elimination:** Remdesivir undergoes metabolism to its active form, GS-441524. The active metabolite has a relatively long half-life, allowing for once-daily dosing. It is primarily eliminated through urine and feces.