

ANTIVIRAL AND ANTIRETROVIRAL DRUGS

University Of Nairobi

Department Of Public Health, Pharmacology & Toxicology

JPT 341 Pharmacology & Toxicology

BVM 3RD Year Lecture Notes

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Lecture objectives

1. By the end of this lecture the students should be able;
 - ❖ To give major groups and specific examples of the antiviral and antiretroviral drugs.
 - ❖ To describe the mechanisms of action of antiviral and antiretroviral drugs including their pharmacological effects.
 - ❖ To outline clinical applications the drugs in vet medicine.

Lecture outline

- **Introduction**
- **Classification of antiviral and antiretroviral drugs**
- **Pyrimidine nucleosides analogues: Idoxuridine**
- **Purine nucleosides analogues: Acyclovir, Ganciclovir**
- **Antiviral prodrugs: Ribavirin and Oseltamivir)**
- **Cyclic amine antiviral drugs: Amantadine**
- **Antiretrovirals: azidothymidine,**
- **Biologic Response Modifiers: Interferon, cytokines.**

Introduction

- Antiviral and antiretroviral agents are compounds active against viruses including retroviruses.
- Since viruses are obligate intracellular microorganisms, drugs that target viral processes must penetrate host cells.
- Therefore, drugs that negatively impact on a virus are also likely to negatively impact normal pathways of the host.
- Consequently, antiviral drugs have a narrow therapeutic margin as compared to antibacterial drugs.

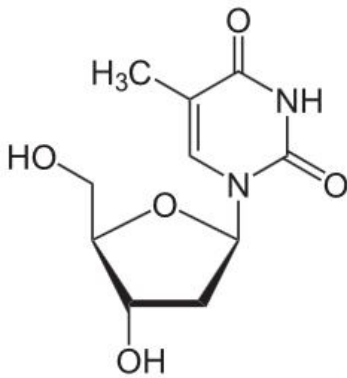
Classification of antifungal drugs

- **Based on chemical structures:** The classes include pyrimidine nucleosides, purine nucleosides analogues and antimetabolites prodrugs.
- **Based on their modification of host biological functions:** Biologic Response Modifiers like cytokines
- **Based on the type of viruses they act on:** DNA based viruses or RNA based retroviruses
- **Miscellaneous antiviral drugs**

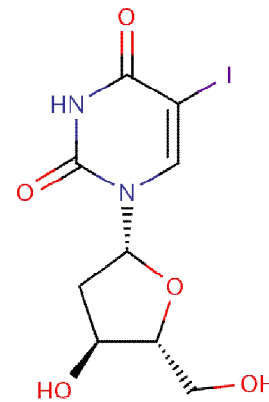
Pyrimidine nucleosides analogues

- Pyrimidine nucleoside analogues mimics pyrimidine nucleosides in their chemical structures and includes **Idoxuridine** and **Trifluridine**.

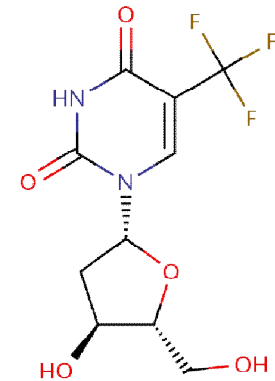
Pyrimidine nucleosides Deoxythymidine analogues



Deoxythymidine



Idoxuridine



Trifluridine

Mechanisms of actions of idoxuridine and trifluridine

- The pyrimidine nucleosides analogues substitute pyrimidine for thymidine, causing defective DNA molecules.
- In particular, idoxuridine inhibits viral replication by substituting itself for thymidine in viral DNA.
- This in turn inhibits the functions of thymidylate phosphorylase and viral DNA polymerases resulting in inability of the virus to reproduce and infect tissue.

Mechanisms of action of idoxuridine and trifluridine

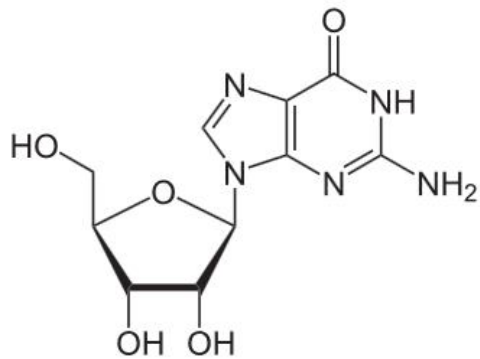
- The mechanism of action of **trifluridine** has not been fully determined, but is thought to inhibit viral replication.
- It does this by incorporating into viral DNA during replication and forms defective proteins and cause an increased mutation rate.
- This drug also reversibly inhibits thymidylate synthetase, an enzyme that is necessary for DNA synthesis.

Clinical applications of idoxuridine and trifluridine

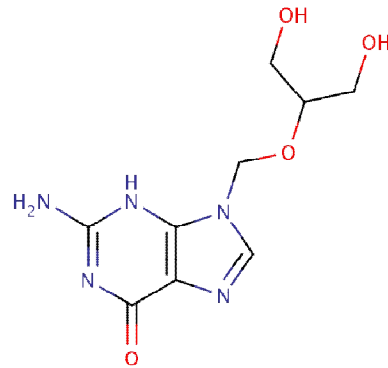
- Idoxuridine is effective against herpesvirus infection of the superficial layers of the cornea (herpesvirus keratitis) and of the skin, but is toxic when administered systemically.
- Trifluridine is the agent of choice for the treatment of herpesvirus keratitis in humans.

Purine nucleosides analogues

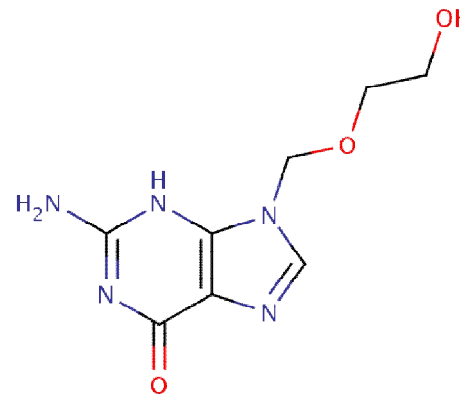
- These purine nucleoside analogues mimics guanosine nucleosides in their chemical structures and includes **vidarabine acyclovir, and ganciclovir.**



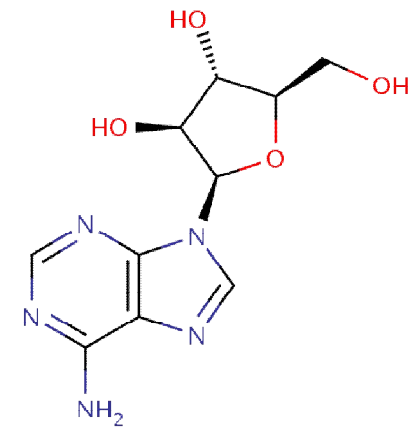
Guanosine



Ganciclovir



Acyclovir,



vidarabine

Mechanisms of actions

- **Vidarabine** is phosphorylated by cellular kinases to a triphosphate compound, which is an inhibitor and a substrate of viral DNA polymerase.
- When used as a substrate for viral DNA polymerase, the phosphorylated compound competitively inhibits dATP leading to the formation of 'faulty' DNA.
- This results in the prevention of DNA synthesis, as phosphodiester bridges can no longer be built, destabilizing the strand

Mechanisms of actions

- Acyclovir is phosphorylated by virus-induced thymidine kinase to the triphosphate form, which is a better substrate and inhibitor of viral DNA polymerase, compared with host.
- Binding to DNA polymerase is irreversible and once incorporated into viral DNA, the DNA chain is terminated.
- The mechanism of action of ganciclovir is similar to that of acyclovir.

Clinical applications

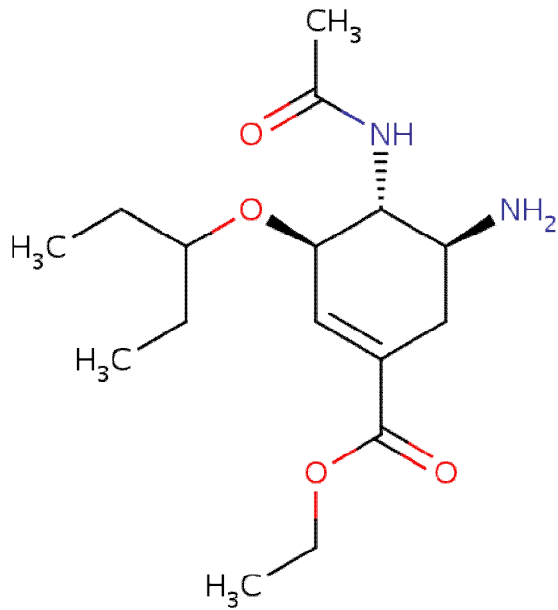
- Herpesviral enzymes are ~20-fold more susceptible to vidarabine compared with host DNA.
- **Vidarabine** is effective against chickenpox - varicella, herpes zoster and herpes simplex.
- **Acyclovir** is useful against the herpesvirus family and is available as an ophthalmic ointment, a topical ointment and cream, an IV preparation, and oral formulations.
- **Ganciclovir** is effective against human cytomegalovirus.

Side effects

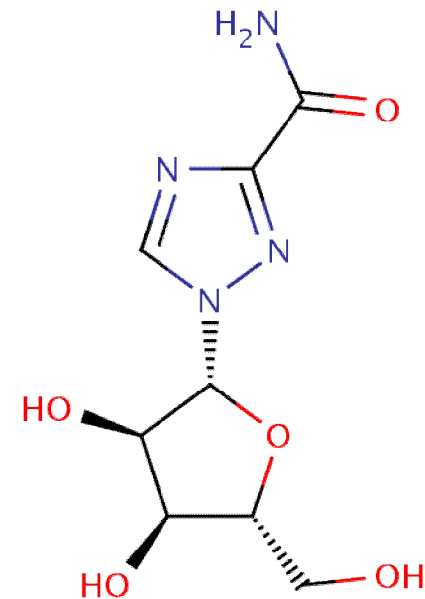
- Ganciclovir use may cause neutropenia and thrombocytopenia, fever, rash, GIT symptoms, confusion and seizure.
- Vidarabine may cause bone marrow suppression and CNS problems when high blood levels are reached.

Antiviral prodrugs

- Ribavirin is a synthetic triazole nucleoside while is Oseltamivir an acetamido cyclohexene that is analogue of sialic acid



Oseltamivir



Ribavirin

Mechanism of action of ribavirin

- Ribavirin is readily phosphorylated intracellularly by adenosine kinase to ribavirin triphosphate.
- Ribavirin triphosphate is a potent competitive inhibitor of inosine monophosphate (IMP) dehydrogenase, viral RNA polymerase and viral mRNA guanylyltransferase.
- Guanylyltransferase inhibition stops the capping of mRNA

Mechanism of action of ribavirin

- This causes a marked reduction of intracellular guanosine triphosphate pools and inhibition of viral RNA and protein synthesis.
- Ribavirin is also incorporated into the viral genome causing lethal mutagenesis and a subsequent decrease in specific viral infectivity.

Clinical uses of ribarivin

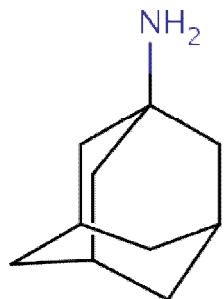
- Ribavirin has a broad spectrum of activity against many RNA and DNA viruses.
- It is active against adenoviruses, herpesviruses, orthomyxoviruses, paramyxoviruses, poxviruses, picornaviruses, rhabdoviruses, rotaviruses, and retroviruses.
- Ribavirin does not have a wide margin of safety in domestic animals

Mechanism of action of oseltamivir

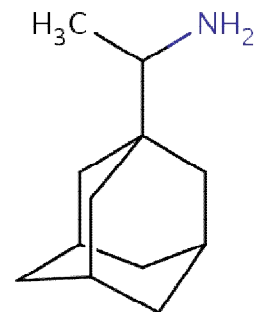
- Oseltamivir is hydrolysed to oseltamivir carboxylate, the active form, which inhibits influenza virus neuraminidase and thus may alter virus particle aggregation and release.
- Oseltamivir (Tamiflu) is effective against influenza infection in and has been used for the prophylaxis of influenza in humansr

Cyclic amine antiviral drugs

- Amantadine and rimantadine, are cyclic amine antiviral drugs.



Amantadine



Rimantadine

Mechanisms of actions of cyclic amine antiviral drugs

- **Amantadine** drug interferes with a viral protein, M2 (an ion channel needed for the viral particle to become "uncoated" once it infects the cell.
- This leads to inhibition or delay of the uncoating process that precedes primary transcription.
- Amantadine may also interfere with the early stages of viral mRNA transcription.

Mechanisms of actions of cyclic amine antiviral drugs

- The mechanism of action of rimantadine is not fully understood.
- It appears to exert its inhibitory effect early in the viral replicative cycle, possibly inhibiting the uncoating of the virus.

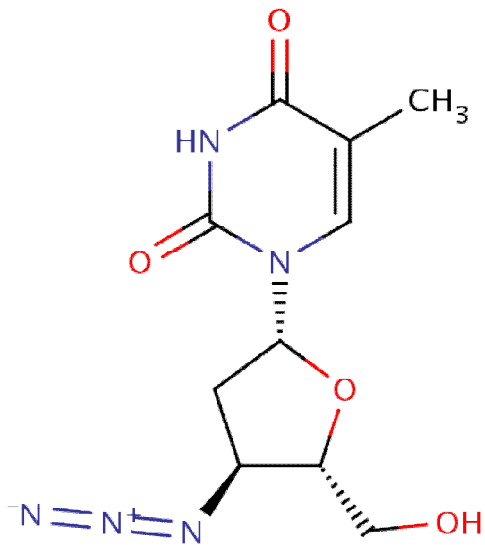
Indications and side effects of amantadine

- Amantadine at usual concentrations inhibits replication of influenza A and C viruses, Sendai virus, and pseudorabies virus.
- It is used clinically to prevent infection with various strains of influenza A viruses.
- It produces few adverse effects, related to the CNS including stimulation of the CNS at very high doses.

Antiretroviral drugs

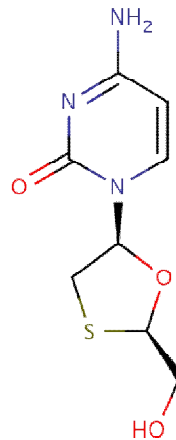
- Antiretroviral drugs are medications for the treatment of infection by retroviruses, primarily HIV.

Thymidine analogue



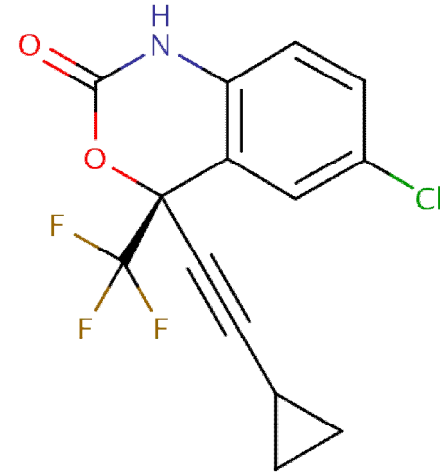
Azidothymidine, AZT

Synthetic nucleoside analogue



Lamivudine

Synthetic purine derivative



Efavirenz

Mechanisms of actions of antiretroviral drugs

- Generally, antiretroviral drugs inhibits **retroviral** reverse transcriptase and subsequent DNA transcription in host cells preventing viral replication.
- In particular, AZT inhibits viral reverse transcriptase, which converted the viral RNA into double-stranded DNA before it is integrated into the host cell genome and prevents viral replication.
- Efavirenz also inhibits the activity of viral reverse transcriptase but the drug must be converted intracellularly to the active triphosphorylated form.

Clinical use of antiretroviral drugs

- These drugs are mainly used in management of HIV and are of limited use in veterinary medicine
- The drugs are effective for acute infections but are relatively ineffective for chronically infected cells because they inhibit early viral replication.
- Granulocytopenia and anemia are the major adverse effects of AZT in human patients

Biologic response modifiers

- Biologic response modifiers include cytokines such as;
 - ❖ Interferons (IFN),
 - ❖ Interleukins (IL),
 - ❖ Hematopoietic growth factors
- Recombinant Interferon Alfa-2a has been produced

Mechanisms of actions of interferon 2 α

- Interferons modulate the host immune response and thus may help in fighting viral infections.
- They bind to receptors on other cells and induce antiviral proteins that protect the cell from infection.
- IFNs also have antitumor, antiparasitic, and immunomodulatory effects.

Clinical application of BRM

- Recombinant Interferon Alfa-2a may be used for treatment of chronic hepatitis C, and oral warts arising from HIV infection.
- In veterinary medicine, Interferon α -2 (3×10^6 IU/vial) may be used to manage feline leukemia virus, feline infectious peritonitis and feline immunodeficiency virus.

References

- Clinical Pharmacology, D.R. LAURENCE & P.N. BENNET
- Veterinary Applied Pharmacology and Therapeutics
- The Merck Veterinaty Manual
- *DrugBank: <http://www.drugbank.ca/drugs/>*