

Antiviral Therapy

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Challenges to the Development of Effective Antiviral Agents

- Myriad number of agents
- Need knowledge of replication at molecular level to define targets
 - Viruses as intracellular parasites make targeting more difficult to avoid host toxicity
- Lack of culture systems for some agents hinders development
- High through-put screening plus 'rational' drug design are both labor intensive and expensive

Challenges to the Development of Effective Antiviral Agents

- Pathogenesis of certain agents makes therapy a challenge even in the face of defined targets
- Clinical presentation of acute viral infections may be at peak of viral replication in vivo
 - May have a small window to intervene effectively
 - Need rapid diagnostic procedures

Diagnosis of Viral Infections

- Clinical suspicion
 - Is syndrome diagnostic of a specific entity?
 - Is viral disease in the differential diagnosis of a presenting syndrome?
- Knowledge of appropriate specimen(s) to send
 - Blood
 - Body fluids
 - Lesion scraping
 - Tissue
 - Proper transport is essential

Herpes Zoster



Progress in Antiviral Therapy

Herpesviruses (HSV, VZV, CMV)	Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir
HIV-1	25 approved agents
Influenza	Amantadine, rimantadine, zanamivir, oseltamivir
Resp. syncytial virus	Ribavirin
Hepatitis B	3TC, FTC, adefovir, tenofovir, entecavir, telbivudine
Hepatitis C	pegIFN-ribavirin
Papillomaviruses	IFN, ?cidofovir
Poxviruses	?Cidofovir
JC virus	?Cidofovir

Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

Anti-Herpesvirus Agents

- Acyclovir
- Valacyclovir
- Famciclovir
- Ganciclovir
- Valganciclovir
- Foscarnet
- Cidofovir
- Formivirsen
- Trifluridine
- Idoxuridine

Anti-Herpesvirus Agents

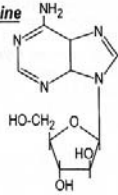
Drug	Description	Active Moiety	Target Agents	Route of Admin	Toxicities
Acyclovir	Acyclic nucleoside	Tri-phosphate	HSV, VZV	Oral, intravenous, topical	Renal, Neuro
Val-ACV	Ester prodrug of acyclovir	Tri-phosphate	HSV, VZV	Oral	Renal, Neuro
Penciclovir	Acyclic nucleoside	Tri-phosphate	HSV	Topical	Local irritation
Famciclovir	Ester prodrug of penciclovir	Tri-phosphate	HSV, VZV	Oral	Headache, nausea
Ganciclovir	Acyclic nucleoside	Tri-phosphate	CMV, HSV, VZV	Intravenous, oral, intraocular	Hematologic
Val-GCV	Ester prodrug of ganciclovir	Tri-phosphate	CMV	Oral	Hematologic

Anti-Herpesvirus Agents

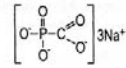
Drug	Description	Active Moiety	Target Agents	Route of Admin	Toxicities
Foscarnet	Pyro-phosphate analog	Parent drug active	CMV, HSV	Intravenous	Renal, metabolic
Cidofovir	Nucleotide analog	Di-phosphate	CMV, HSV, HPV, pox	Intravenous	Renal, ocular
Formivirsen	Antisense oligo-NT: binds to CMV mRNA	Parent drug active	CMV	Intraocular	Ocular
Trifluridine	Nucleoside analog	Tri-phosphate	HSV keratitis	Topical	Ocular
Idoxuridine	Nucleoside analog	Tri-phosphate	HSV keratitis	Topical	Ocular

Anti-Herpesvirus Agents

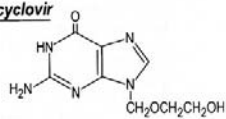
Vidarabine



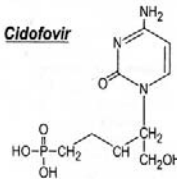
Foscarnet



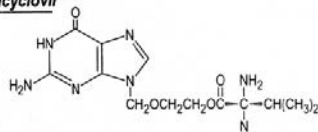
Acyclovir



Cidofovir

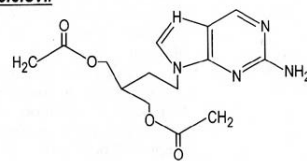


Valacyclovir

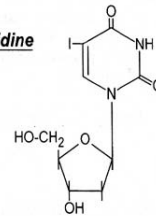


Anti-Herpesvirus Agents

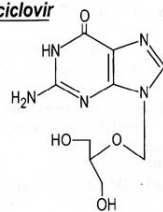
Famciclovir



Idoxuridine



Ganciclovir



Trifluridine

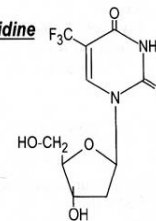
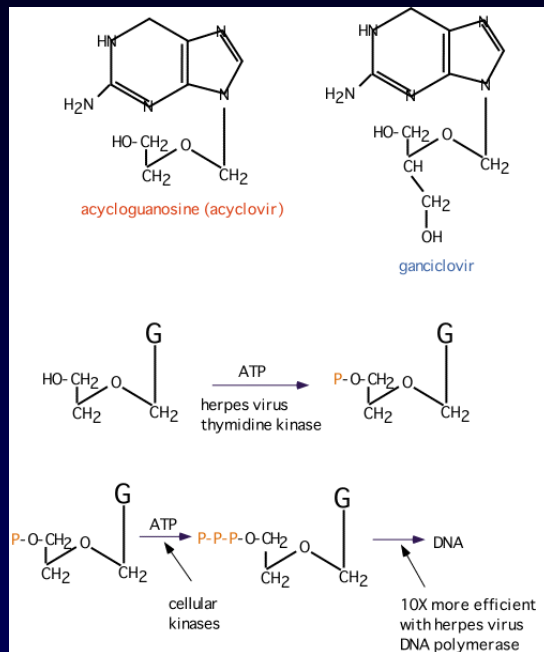


FIGURE 11-1. Chemical structures of antitherpesviral agents.

Acyclovir I

- Development represents a watershed in the field of antiviral chemotherapy
- Acyclic guanosine analog
- Active vs. HSV, VZV and modestly CMV
- Mechanism of action
 - Preferentially taken up by virally infected cells
 - Monophosphorylated by virally encoded thymidine kinases
 - Di- and triphosphorylation completed by cellular kinases
 - ACV-TP is the active moiety
 - Competitive inhibitor of viral DNA polymerase
 - Cellular DNA polymerases much less susceptible to inhibition
 - Leads to viral DNA chain termination

Acyclovir: Mechanism of Action



Acyclovir II

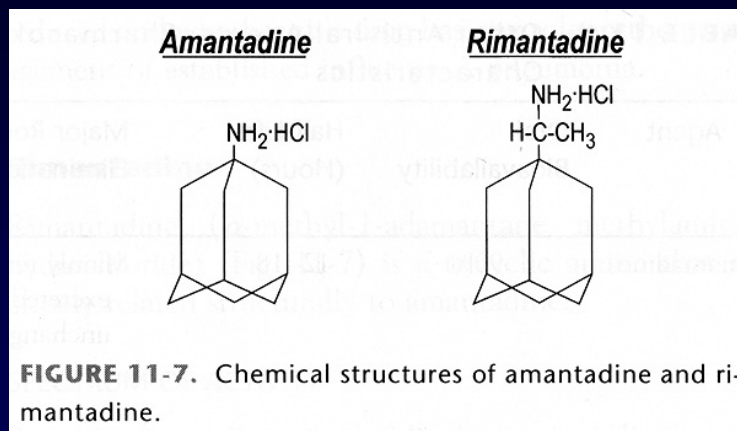
- **Pharmacology**
 - Administered by oral, intravenous and topical routes
 - Oral bioavailability 15-30%
 - $T_{1/2}$ 3 hrs
 - Primarily renally excreted
- **Toxicities**
 - Headache, nausea
 - Renal
 - Neurologic
- **Resistance**
 - Mediated by mutations in viral thymidine kinase and/or viral DNA polymerase genes
 - TK-deficient and TK altered virus can be produced
 - Clinically significant infections can be caused by drug resistant HSV and VZV

Anti-Respiratory Virus Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

Amantadine and Rimantadine

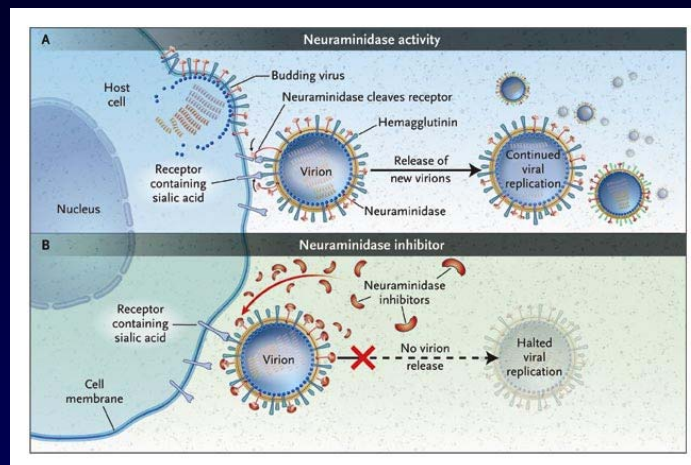
- Tricyclic amines
- Active vs. influenza A only at clinically achievable concentrations
- Mechanism of action
 - Interference with function of viral M2 protein
 - M2 protein acts as an ion channel facilitating the hydrogen ion mediated dissociation of the matrix protein from the nucleocapsid
- Pharmacology:
 - Orally bioavailable
 - Amantadine: renal excretion
 - Rimantadine: hepatic metabolism and renal excretion
- Major toxicity
 - Neurotoxicity: amantadine > rimantadine
- Useful for treatment and prophylaxis of influenza A infections
 - Should not be used when amantadine resistant strains are in circulation
- Resistance mediated by mutations in M2 coding region



Zanamivir and Oseltamivir I

- Active vs. influenza A and B
- Mechanism of action
 - Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces
 - Neuraminidase inhibitors thus prevent release of virions from infected cell

Mechanism of Action of Neuraminidase Inhibitors

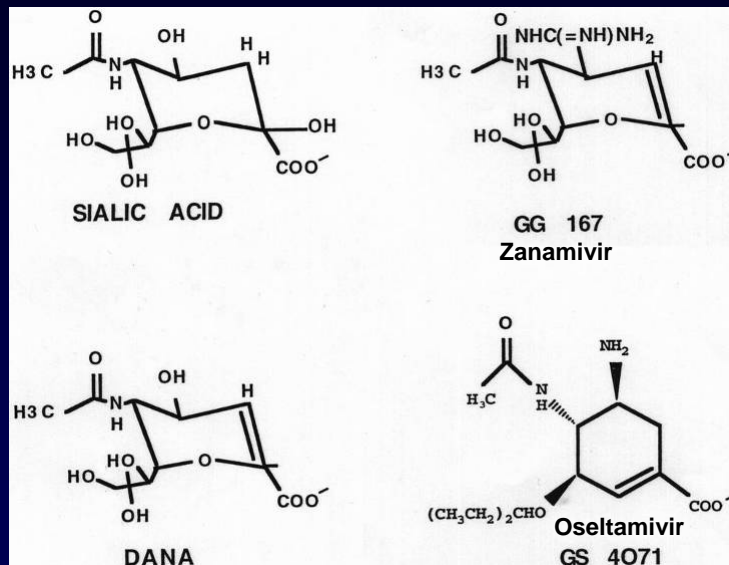


Moscona, A. N Engl J Med 2005;353:1363-1373

Zanamivir and Oseltamivir II

- Pharmacology
 - Zanamivir
 - Oral inhalation
 - Oseltamivir
 - Orally bioavailable
 - Converted from ester prodrug to active form
 - Renally excreted
- Toxicities
 - Exacerbation of reactive airway disease by zanamivir
 - Nausea and vomiting for oseltamivir

Zanamivir and Oseltamivir III



Zanamivir and Oseltamivir IV

- **Indications**
 - Treatment of influenza A and B within 24-48 hrs of symptom onset
 - Prophylaxis
 - N.B.: Neither drug interferes with antibody response to influenza vaccination
- **Resistance**
 - Incidence appears to be increasing
 - Ongoing surveillance necessary

Ribavirin I

- **Synthetic nucleoside analog**
- **Active vs. broad range of RNA and DNA viruses**
 - Flavi-, paramyxo-, bunya-, arena-, retro-, herpes-, adeno-, and poxviruses
- **Mechanism of action complex**
 - Triphosphorylated by host cell enzymes
 - **For influenza**
 - Ribavirin-TP interferes with capping and elongation of mRNA and may inhibit viral RNA polymerase
 - **For other agents**
 - Ribavirin-MP inhibits inosine-5'-monophosphate dehydrogenase depleting intracellular nucleotide pools, particularly GTP

Ribavirin II

- **Pharmacology**
 - Aerosol and oral administration
 - Hepatically metabolized and renally excreted
- **Major toxicity**
 - Anemia
- **Indications**
 - Aerosol treatment of RSV in children
 - Effectiveness debated
 - Oral treatment of HCV (in combination with pegylated IFN-alpha)

Anti-Hepatitis B Virus Agents

- Interferon-alpha (pegylated)
- Lamivudine (3TC)
 - Nucleoside analog first developed for HIV
 - Lower dose used for HBV (100 mg/day)
- Emtricitabine (FTC)
 - Anti-HIV nucleoside analog with strong anti-HBV activity
- Adefovir dipivoxil
 - Nucleotide analog first developed for HIV but nephrotoxic at higher doses
 - Approved for HBV at lower dose (10 mg/day)
- Entecavir
 - Nucleoside analog with activity originally thought limited to HBV but recent reports indicate entecavir also has anti-HIV-1 activity and can induce resistance in HIV-1
 - Approved for use at dose of 0.5-1.0 mg/day
- Telbivudine
 - Nucleoside (thymidine) analog with activity vs. HBV but not HIV
 - Recently approved at a dose of 600 mg/day

Anti-Hepatitis C Virus Agents

- **Approved**
 - Interferon-alpha (pegylated)
 - Ribavirin
- **In development**
 - Protease inhibitors
 - Polymerase inhibitors

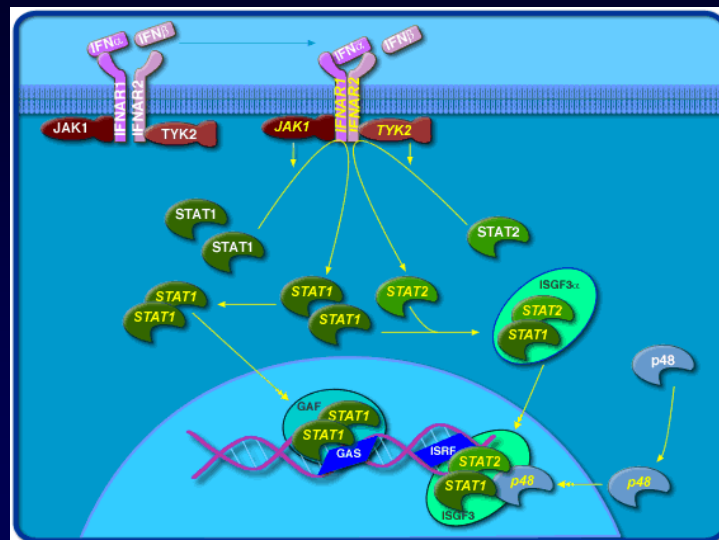
Interferons I

- Part of cytokine repertoire
- Possess antiviral, immunomodulatory and antiproliferative effects
- **Types**
 - **Alpha/Beta (leukocyte/fibroblast)**
 - Coding genes located on chromosome 9
 - At least 24 subtypes of alpha, 1 of beta
 - **Gamma**
 - Coding gene located on chromosome 12
 - 1 subtype

Interferons II: Mechanism of Action

- Act by inducing an antiviral state within cells
- Bind to specific receptors on cell surface
- Receptor associated tyrosine kinases activated
 - Tyk2 and JAK 1 for alpha and beta
 - JAK1 and JAK2 for gamma
- Cytoplasmic proteins [signal transducers and activators of transcription (STAT)] phosphorylated
 - Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes

Interferon Mechanism



Interferons III: Mechanisms of Action

- **Synthesis of 2'-5' oligoadenylate synthetase**
 - Activated by dsRNA
 - Convert ATP into a series of 2'-5' oligo(A)s
 - These activate RNAase L which cleaves single stranded mRNAs
- **Synthesis of dsRNA-dependent protein kinase (PKR, eIF-2 kinase)**
 - PKR activated by dsRNA and autophosphorylated
 - In turn, phosphorylates alpha subunit of eukaryotic initiation factor 2
 - Protein synthesis inhibited
- **Induction of a phosphodiesterase with inhibition of peptide chain elongation**
- **Synthesis of MxA protein which can bind to cytoskeletal proteins and inhibit viral transcriptases**
- **Induction of nitric oxide by gamma IFN in macrophages**

Interferons IV

- **Pharmacology**
 - Injected IM or SC
 - Renal excretion and inactivation in body fluids/tissues
- **Toxicities**
 - Flu-like symptoms
 - Hematologic effects
 - Leukopenia and thrombocytopenia
 - Neuropsychiatric effects
- **Antiviral indications**
 - IFN-alpha (pegylated) SC for HCV (in combination with ribavirin)
 - Intralesional for condyloma acuminata
- **Resistance can develop**
 - Mutations in NS5A gene of HCV described

Passive Immunization for Viral Infections I

- **Human immune globulin**
 - Prevention of hepatitis A
 - Prophylaxis and treatment of enterovirus infections in neonates and in children with antibody deficiency
 - Treatment of B19 parvovirus infection in immunodeficient individuals
- **CMV immune globulin**
 - Prophylaxis of CMV in solid organ transplant recipients
 - Treatment of CMV pneumonia in combination with ganciclovir
- **Hepatitis B immune globulin**
 - Prophylaxis of hepatitis B infection
- **Rabies immune globulin**
 - Post-exposure prophylaxis for rabies (in combination with rabies vaccine)

Passive Immunization for Viral Infections II

- **Respiratory syncytial virus immune globulin**
 - Prevention of complications of RSV infection in young children
- **Palivizumab**
 - Humanized RSV monoclonal antibody
 - Prevention of complications of RSV infection in young children
- **Varicella-zoster immune globulin**
 - Prevention of varicella infection in immunocompromised children and adults within 96 hours of exposure
- **Vaccinia immune globulin**
 - Available from CDC for complications of smallpox (vaccinia) vaccination

Conclusions

- Field of antiviral therapy has matured dramatically in past 30+ years
- Greatest progress made for
 - Herpesviruses
 - HIV
 - Respiratory viruses
 - Hepatitis viruses
- Preventive vaccination remains the key to global control of viral infections