Antiviral Agents

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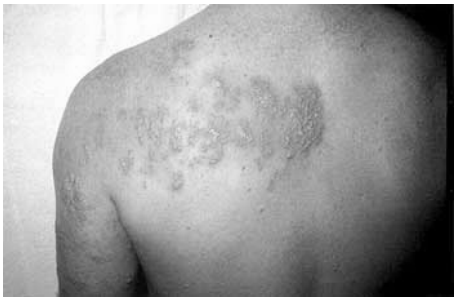
Diagnosis of Viral Infections

- 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

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

Herpes Zoster



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

Progress in Antiviral Therapy

Herpesviruses (HSV, VZV, CMV)	Acyclovir, famciclovir, valacyclovir, ganciclovir, cidofovir, formivirsen, valganciclovir
HIV-1	21 approved agents
Influenza	Amantadine, rimantadine, ribavirin, zanamivir, oseltamivir
Resp. syncytial virus	Ribavirin, RSV immune globulin, palivizumab
Hepatitis B	3TC, FTC, adefovir, tenofovir, entecavir
Hepatitis C	pegIFN-ribavirin
Papillomaviruses	IFN, ?cidofovir
JC virus	?Cidofovir
Picornaviruses	Pleconaril
Rhinoviruses	Tremacamra (rsICAM-1)

Non-HIV Antiviral Therapy: Targets

- Herpesviruses
- Respiratory viruses
- Hepatitis viruses
- Others

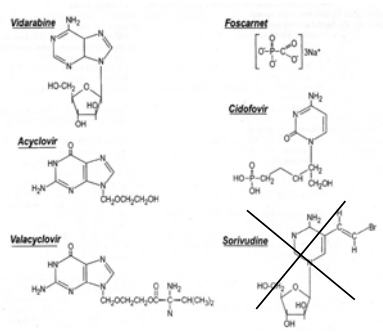
Anti-Herpesvirus Agents

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

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

Anti-Herpesvirus Agents



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

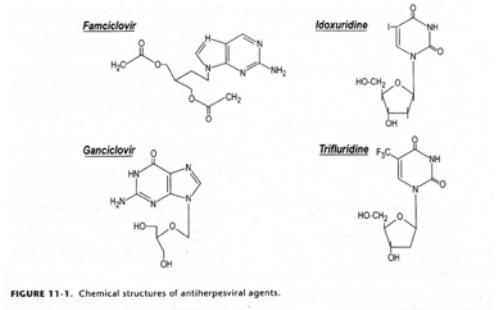


FIGURE 11-1. Chemical structures of antiherpesviral agents.

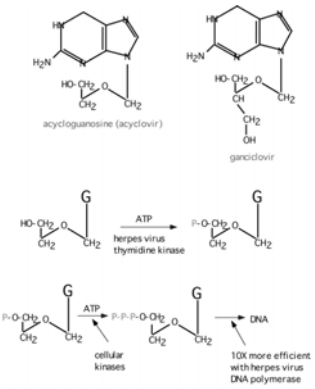
Acyclovir I

- 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

Anti-Respiratory Virus Agents

- Amantadine
- Rimantadine
- Zanamivir
- Oseltamivir
- Ribavirin

Acyclovir: Mechanism of Action



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
- Resistance mediated by mutations in M2 coding region

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

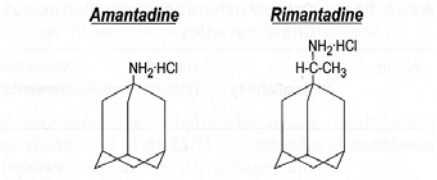


FIGURE 11-7. Chemical structures of amantadine and rimantadine.

Influenza Virus Replication Cycle

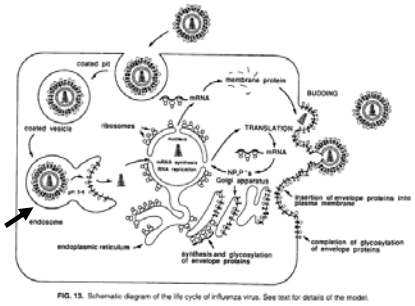


FIG. 13. Schematic diagram of the life cycle of influenza virus. See text for details of the model.

From Fields *Virology*

Influenza Virus Replication Cycle

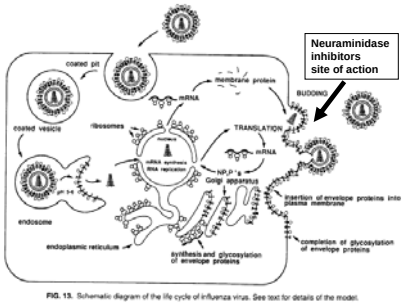


FIG. 13. Schematic diagram of the life cycle of influenza virus. See text for details of the model.

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Uncoating of Influenza Virus

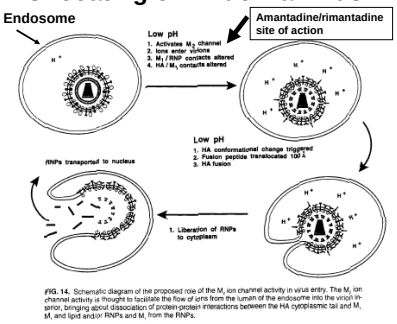


FIG. 14. Schematic diagram of the proposed role of the M_2 ion channel activity in virus entry. The M_2 ion channel activity is thought to facilitate the flow of ions from the lumen of the endosome into the virion interior, bringing about dissociation of protein-protein interactions between the HA cytoplasmic tail and M_1 and lipid and/or RNPs and M_1 from the RNPs.

From Fields *Virology*

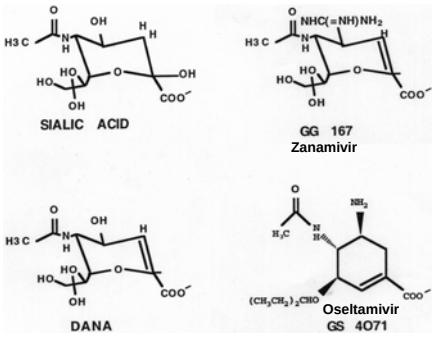
Zanamivir and Oseltamivir II

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

Zanamivir and Oseltamivir I

- **Active vs. influenza A and B**
- **Mechanism of action**
  - **Neuraminidase inhibitors**
    - **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**
  - **Oseltamivir is an ester prodrug of GS4071, oseltamivir carboxylate**
    - **Transition state analog of sialic acid**
      - **Binds to viral neuraminidase**

Zanamavir and Oseltamivir III



Zanamivir and Oseltamivir IV

- **Indications**
  - **Treament 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**
  - **Reports beginning to appear in literature**

Anti-Hepatitis Agents

- **Hepatitis B**
  - **Lamivudine**
    - **Nucleoside analog first developed for HIV**
    - **Lower dose used for HBV (100 mg/day)**
  - **Adefovir dipivoxil**
    - **Nucleotide analog first developed for HIV but nephrotoxic at higher doses**
    - **Approved for HBV at lower dose (10 mg/day)**
  - **Entecavir**
    - **Most recently approved anti-HBV agent**
- **Hepatitis C**
  - **Interferon-alpha (pegylated)**
  - **Ribavirin**

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**

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**

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)**

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 (STAT) phosphorylated**
  - **Move to nucleus and bind to cis-acting elements in promoter regions of IFN inducible genes**

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