Pharmacology of Antiviral Agents & Local Anesthetics

Abdelkader Ashour, Ph.D.

Antiviral Agents
Antiviral Agents, Overview

- Viruses are obligate intracellular parasites
- Viral replication depends primarily on synthetic processes of the host cell
- To be effective, antiviral agents must either:
  - block viral entry into the cell
  - block viral exit from the cell
  - be active inside the host cell
- As a result, nonselective inhibitors of virus replication may interfere with host cell function and produce toxicity

Acyclovir, Overview

- Acyclovir is an acyclic guanosine derivative with clinical activity against Herpes Simplex Virus (HSV-1), HSV-2 and Varicella Zoster Virus (VZV)

Pharmacokinetics

- The bioavailability of oral acyclovir is 15–20% and is unaffected by food.
- Peak serum concentrations are reached 1.5–2 hours after dosing.
- Acyclovir is cleared primarily by glomerular filtration and tubular secretion. The half-life is approximately 3 hours in patients with normal renal function and 20 hours in patients with anuria.
- Topical formulations produce high local concentrations in herpetic lesions, but systemic concentrations are undetectable.
- Acyclovir diffuses into most tissues and body fluids to produce concentrations that are 50–100% of those in serum. Cerebrospinal fluid concentrations are 50% of serum values.
I. Acyclovir requires three phosphorylation steps for activation.
   – It is converted first to the monophosphate derivative by the virus-specified thymidine kinase
   – then to the di- and triphosphate compounds by the host’s cellular enzymes
   ♦ Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated and accumulates only in infected cells

II. Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms:
   1. Competitive inhibition with deoxyGTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex
   2. Chain termination following incorporation into the viral DNA

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**Acyclovir, Clinical Uses**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Route of Administration</th>
<th>Use</th>
<th>Recommended Adult Dosage and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acyclovir^1</td>
<td>Oral</td>
<td>First episode genital herpes</td>
<td>400 mg tid or 200 mg five times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent genital herpes</td>
<td>400 mg tid or 200 mg five times daily or 800 mg bid</td>
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<tr>
<td></td>
<td></td>
<td>Genital herpes suppression</td>
<td>400 mg bid</td>
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<tr>
<td></td>
<td></td>
<td>Herpes zoster</td>
<td>400 mg five times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mucocutaneous herpes in the immunocompromised host</td>
<td>400 mg five times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Varicella</td>
<td>20 mg/kg (maximum 800 mg) four times daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zoster</td>
<td>800 mg five times daily</td>
</tr>
</tbody>
</table>

**Intravenous**

<table>
<thead>
<tr>
<th>Use</th>
<th>Dosage and Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe HSV infection</td>
<td>5 mg/kg q8h</td>
</tr>
<tr>
<td>Herpes encephalitis</td>
<td>10–15 mg/kg q8h</td>
</tr>
<tr>
<td>Neonatal HSV infection</td>
<td>50 mg/kg q8h</td>
</tr>
<tr>
<td>Varicella or zoster in the immunocompromised host</td>
<td>10 mg/kg q8h</td>
</tr>
</tbody>
</table>

➢ N.B. Topical acyclovir is much less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrences.
Acyclovir, Resistance and Adverse Effects

- **Resistance**
  - Resistance to acyclovir can develop in HSV or VZV through alteration in either the viral thymidine kinase or the DNA polymerase
  - Agents such as foscarnet, cidofovir, and trifluridine do not require activation by viral thymidine kinase and thus have preserved activity against the most prevalent acyclovir-resistant strains

- **Adverse Effects**
  - Acyclovir is generally well tolerated. Nausea, diarrhea, and headache have occasionally been reported
  - I.v. infusion may be associated with reversible renal dysfunction due to crystalline nephropathy or neurologic toxicity (e.g., tremors, delirium, seizures); however, these are uncommon with adequate hydration and avoidance of rapid infusion rates
  - Chronic daily suppressive use of acyclovir for more than 10 years has not been associated with untoward effects

Zidovudine, Overview

- Zidovudine (azidothymidine; AZT) is a deoxythymidine analog
- Zidovudine is the first licensed antiretroviral agent. It is the first drug approved for treatment of HIV

- **Mechanism of Action**
  - Intracellularly, zidovudine is phosphorylated to its active 5-triphosphate metabolite, zidovudine triphosphate (AZT-TP)
  - Zidovudine acts by competitive inhibition of HIV-1 reverse transcriptase (RT; the enzyme that HIV uses to make a DNA copy of its RNA)
    - The RT uses zidovudine triphosphate instead of thymidine triphosphate for making DNA, and it is the zidovudine triphosphate that interferes with the RT
  - Zidovudine can also be incorporated into the growing viral DNA chain to cause termination

- **Pharmacokinetics**
  - It is well absorbed from the gut and distributed to most body tissues and fluids, including the cerebrospinal fluid
  - Plasma protein binding is approximately 35%
  - The serum half-life averages 1 hour, and the intracellular half-life of the phosphorylated compound is 3.3 hours
  - Zidovudine is eliminated primarily by renal excretion following glucuronidation in the liver
Zidovudine, Clinical Uses

- Zidovudine has been shown to decrease the rate of clinical disease progression and prolong survival in HIV-infected individuals
  - Efficacy has also been demonstrated in the treatment of HIV-associated dementia and thrombocytopenia
- In pregnancy, a regimen of oral zidovudine beginning between 14 and 34 weeks of gestation (100 mg five times a day), i.v. zidovudine during labor (2 mg/kg over 1 hour, then 1 mg/kg/h by continuous infusion), and zidovudine syrup to the neonate from birth through 6 weeks of age (2 mg/kg every 6 hours) has been shown to reduce the rate of vertical (mother-to-newborn) transmission of HIV by up to 23%

Zidovudine, Resistance and Adverse Effects

- Resistance
  - Resistance may occur by mutations in the HIV-1 RT gene resulting in 6 amino acid substitutions (M41L, D67N, K70R, L210W, T215Y or F, and K219Q) that confer zidovudine resistance
  - In general, higher levels of resistance were associated with greater number of mutations

- Adverse Effects
  - The most common adverse effect of zidovudine is myelosuppression, resulting in anemia or neutropenia
  - GI intolerance, headaches, and insomnia may occur but tend to resolve during therapy.
  - Less frequent side effects include:
    - Thrombocytopenia, hyperpigmentation of the nails, and myopathy. Very high doses can cause anxiety, confusion, and tremulousness.
    - Increased serum levels of zidovudine may occur with concomitant administration of probenecid, phenytoin, methadone, fluconazole, atovaquone, valproic acid, and lamivudine, either through inhibition of first-pass metabolism or through decreased clearance
    - Zidovudine may decrease phenytoin levels, and this warrants monitoring of serum phenytoin levels in epileptic patients taking both agents.
    - Hematologic toxicity may be increased during coadministration of other myelosuppressive drugs such as ganciclovir, ribavirin, and cytotoxic agents
Interferon Alfa, Overview

- Interferons are naturally occurring small proteins that exert complex antiviral, immunomodulatory, and antiproliferative activities through cellular metabolic processes involving synthesis of both RNA and protein.
- Interferons belong to the large class of glycoproteins known as cytokines.
- Interferons are produced and secreted by cells in response to viral or bacterial infections and to synthetic or biological inducers (e.g. IL-2, IL-12, TNF).

Natural Function:
- Interferons are antiviral and possess anti-oncogenic properties.
- They activate macrophage and natural killer lymphocyte.
- They enhance MHC I and II, and thus presentation of foreign peptides to T cells.

Pharmacokinetics:
- Maximum serum concentrations occur approximately 4 hours after intramuscular administration and approximately 7 hours after subcutaneous administration.
- Elimination half-life is 2–5 hours depending on the route of administration.
- Alfa interferons are filtered at the glomeruli and undergo rapid proteolytic degradation during tubular re-absorption, such that detection in the systemic circulation is negligible.
- Liver metabolism and subsequent biliary excretion are considered minor pathways.

Interferon Alfa, Mechanism of Action and Indications

- Interferons exert their cellular activities by binding to specific membrane receptors (interferon receptors) on the cell surface.
- Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events, including:
  - The induction of certain enzymes such as PKR (phosphorylates and inhibits eIF-2. This inhibits normal cell ribosome function, killing both the virus and the host cell).
  - Suppression of cell proliferation.
  - Immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, up-regulation of MHC I and II, and thus presentation of foreign peptides to T cells.
  - Inhibition of virus replication in virus-infected cells.

Clinical Uses:
- Treatment of both HBV and HCV virus infections.
  - Interferon alfa-2b is the only preparation licensed for treatment of HBV infection and for acute hepatitis C. Interferon alfa-2b leads to loss of HBeAg, normalization of serum aminotransferases, and sustained histologic improvement in approximately one-third of patients with chronic hepatitis B, thus reducing the risk of progressive liver disease.
- Treatment of Hairy cell leukemia.
- As an adjuvant to surgical treatment of malignant melanoma.
- Treatment of clinically aggressive follicular lymphoma.
- Treatment of AIDS-Related Kaposi’s Sarcoma.
Interferon Alfa, Adverse Effects

- A flu-like syndrome within 6 hours after dosing in more than 30% of patients that tends to resolve upon continued administration.
- Other potential adverse effects include thrombocytopenia, granulocytopenia, elevation in serum aminotransferase levels, induction of auto-antibodies, nausea, fatigue, headache, arthralgias, rash, alopecia, anorexia, hypotension, and edema.
- Severe neuropsychiatric side effects may occur.
- Absolute contraindications to therapy are psychosis, severe depression, uncontrolled seizures, neutropenia, thrombocytopenia, decompensated cirrhosis, and a history of organ transplantation (other than liver).
- Alfa interferons are abortifacient in primates and should not be administered in pregnancy.

Local Anesthetics
Action Potential

- Action Potential
  - Depolarization
  - Repolarization
  - Overshoot
  - Latent period
  - After-depolarization
  - After-hyperpolarization

- Stimulator
- CRO
- Axon
- Microelectrode inside axon

Action Potential

- Opening of voltage-gated Na⁺ channels in membrane
- Decreased membrane potential (depolarization)
- Increased Na⁺ permeability
- Increased flow of Na⁺ into cell
- Direction of propagation
- ECF
- Axon
- Myelin
- Active node
- Inactive node
Local Anesthetics, Overview

- Local anesthetics reversibly block impulse conduction along nerve axons and other excitable membranes. This action can be used clinically to block pain sensation from specific areas of the body without the loss of consciousness.

- Cocaine, the first such agent, was isolated by Niemann in 1860. It was introduced into clinical use by Koller in 1884 as an ophthalmic anesthetic.

- Cocaine was soon found to be strongly addicting but was widely used, nevertheless, for 30 years, since it was the only local anesthetic drug available.

- In an attempt to improve the properties of cocaine, Einhorn in 1905 synthesized procaine, which became the dominant local anesthetic for the next 50 years.

- Since 1905, many local anesthetic agents have been synthesized. The goals of these efforts were reduction of local irritation and tissue damage, minimization of systemic toxicity, faster onset of action, and longer duration of action.

- Lidocaine, still a popular agent, was synthesized in 1943 by Löfgren and may be considered the prototype local anesthetic agent.

Lidocaine

- Lidocaine is a common local anesthetic and anti-arrhythmic drug.

- **Pharmacokinetics**
  - Lidocaine is completely absorbed following parenteral administration.
  - The rate of absorption depends on the dose, route of administration, and the vascularity of the injection site.
  - Absorption is considerably slowed by the addition of epinephrine.
  - The clearance of lidocaine is almost entirely due to liver metabolism, and depends both on liver blood flow and the activity of metabolizing enzymes.
  - The half-life may be prolonged two-fold or more in patients with liver dysfunction.

- **Mechanism of Action:**
  - Lidocaine blocks the generation and conduction of impulses through nerve fibers.
  - Lidocaine blocks conduction of nerve impulses by decreasing permeability of the nerve cell membrane to sodium ions, thereby decreasing the rate of depolarization of the nerve membrane, increasing the threshold for electrical excitability, and preventing propagation of the action potential and effecting local anesthetic action.
Lidocaine

**Clinical Uses**
- Lidocaine is used topically to relieve itching, burning and pain from skin inflammations, injected as a dental anesthetic, and in minor surgeries.
- Lidocaine hydrochloride in anesthesia: It is used for infiltration anesthesia and for nerve block techniques including peripheral, sympathetic, epidural, and spinal block anesthesia.
- Lidocaine has been administered intraperitoneally for anesthesia of the peritoneum and pelvic viscera.

**Adverse Effects:** These adverse experiences are, in general, dose-related and may result from high plasma levels caused by overdosage, rapid absorption, or inadvertent intravascular injection, or may result from a hypersensitivity, idiosyncrasy or diminished tolerance on the part of the patient.
- **Common:**
  - Vascular disorders: hypotension, hypertension
  - Cardiac disorders: bradycardia
  - Gastrointestinal disorders: nausea, vomiting
  - Nervous system disorders: paresthesia, dizziness
- **Uncommon:**
  - Nervous system disorders: Signs and symptoms of CNS toxicity (convulsions, numbness of the tongue, visual disturbances, tremor, tinnitus)