Drugs for Influenza and CMV Retinitis

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Antiviral agents are chemotherapeutic drugs that are effective against different viruses. Influenza is a common infection; anti-influenza agents are useful for both prophylaxis and the treatment of influenza. CMV retinitis is a common opportunistic infection in immunocompromised patients; there are several antiviral drugs effective against CMV. Pharmacology of all the drugs will be discussed briefly.

Anti-Influenza Drugs

Amantadine and Rimantadine

Tricyclic amines are effective against only influenza A, not influenza B.

They act by blocking M2 proton ion channels within the viral membrane to prevent acidification of the virus core, prevent ‘uncoating’ – an early step in replication and prevent activation of RNA transcriptase of the virus.

Amantadine is excreted unchanged in urine, hence a dose reduction is required in the elderly and renal insufficiency.
Rimantadine is an α-methyl derivative of amantadine with 4-10 times more anti-influenza activity in vitro, longer half-life, and **hepatic metabolism**; dose reduction is required in hepatic insufficiency, but not in **renal failure**.

One hundred per cent of seasonal H3N2 and 2009 pandemic flu samples tested have shown resistance to rimantadine and it is no longer recommended to prescribe for treatment of the flu.

If initiated before exposure to influenza A, they are very effective in preventing infection (if no resistance), and if initiated within 1-2 days after the onset of illness, they reduce the duration of the symptoms by 1-2 days.

Common adverse effects are nausea, anorexia, insomnia, nervousness, light-headedness, difficulty in concentration, slurred speech, dizziness, ataxia, and **teratogenicity**.

Serious neurological side effects (hallucinations, agitation, behavioral changes, seizures and delirium) can occur due to altered dopamine neurotransmission; are more common with amantadine than with rimantadine, in elderly, renal insufficiency, **seizure disorders**, and with the co-administration of certain drugs (antihistamines, anticholinergics, hydrochlorothiazide, trimethoprim-sulfamethoxazole).

Acute amantadine overdose can present with **anticholinergic symptoms**.

M2 protein is a mutation-prone site; resistance to both the drugs develops rapidly in up to 50% of the treated persons.

**Neuraminidase inhibitors (Oseltamivir & Zanamivir)**

Sialic acid analogs that are active against both influenza A and influenza B viruses.

They reversibly and competitively inhibit **viral neuraminidase and prevent the cleavage of sialic acid residues**, causing clumping of newly released virions to each other and to the membrane of the infected cells. They prevent the spread of infection within the respiratory tract by interfering with the release of **progeny** of influenza virus within the mucosal secretions and reducing viral infectivity.

Oseltamivir (FDA approved for age ≥ 1 year) is an orally administered prodrug, activated by **hepatic esterases**, and excreted by filtration and tubular secretion in kidneys; dose reduction is required in **renal insufficiency**.

Important adverse effects of oseltamivir are nausea, vomiting, abdominal pain, and rarely rash; diarrhea, headache and fatigue are more common when taken prophylactically. **Transient neuropsychiatric** events, like self-injury or delirium, have been reported in Japanese individuals.

Zanamivir (FDA approved for age ≥ 7 years) is administered intranasally; ~10-20% of the drug reaching the lungs and the remainder being deposited in the oropharynx. ~5-15% of the dose undergoes **systemic absorption**, followed by **excretion in urine** with minimal metabolism.

Important adverse effects of zanamivir are coughing, bronchospasm, transient discomfort in nose and throat, reversible decrease in lung function; the drug should not be administered in patients with an underlying airway disease.

If initiated before exposure to the influenza virus, they are very effective in preventing infection, and, if initiated within 36-48 hours after the onset of illness, they reduce the
duration of the illness by 1-2 days, and reduce the severity of symptoms and decrease secondary complications.

Resistance to neuraminidase inhibitors can develop due to point mutations in viral hemagglutinin or neuraminidase genes, but worldwide resistance is rare at present.

Peramivir

A cyclopentane analog, a neuraminidase inhibitor with activity against both influenza A and influenza B viruses.

It received temporary FDA authorization due to the H1N1 pandemic, although it is currently not licensed in the United States.

It is available for intravenous administration and important side effects are nausea, vomiting, diarrhea and neutropenia.

Drugs for the Treatment of CMV Retinitis

CMV (Cytomegalovirus) is a DNA virus which causes asymptomatic infection or a mononucleosis-like syndrome in immunocompetent hosts, but causes opportunistic infection of multiple organ systems, including necrotizing retinitis, in immunocompromised hosts. CMV retinitis is usually seen in patients with AIDS, organ transplants, or those on immunosuppressive treatments.

Treatment of sight-threatening lesions (adjacent to optic nerve or fovea) requires intravitreal injections of ganciclovir or foscarnet for 7-10 days, plus systemic therapy with valganciclovir (preferred) or ganciclovir (alternative). Peripheral lesions are treated by systemic therapy with one of the effective agents.

Ganciclovir

A guanosine analog that, after activation by phosphorylation, inhibits viral DNA polymerase and causes a chain termination of CMV.

In addition to CMV, has in vitro activity against herpes simplex virus (HSV), varicella zoster virus (VZV), Epstein-Barr virus (EBV), human herpes virus (HHV)-6 and HHV-8.

Oral bioavailability is ~10% and renal elimination is directly proportionate to creatinine clearance.

Intravenous ganciclovir is used to delay the progression of CMV retinitis in patients with AIDS; combination therapy with foscarnet is more effective. The induction therapy is followed by maintenance therapy with oral ganciclovir.

Intraocular administration via intravitreal injection or intraocular implant is possible; intraocular implant delays the progression of CMV retinitis to a greater degree than systemic ganciclovir. The implant needs to be replaced at intervals of 5-8 months.

The most common side effect of intravenous ganciclovir is myelosuppression (less with oral form) causing leukopenia and thrombocytopenia; other important adverse effects are fever, rash, mucositis, headache, nausea, diarrhea, hepatic dysfunction, seizures, and peripheral neuropathy.

Resistance can develop due to UL97 mutation (resistance to ganciclovir only) or UL54
mutation (associated with cross-resistance with cidofovir and foscarnet).

Valganciclovir

A prodrug that is rapidly hydrolyzed by esterases in the intestinal wall and liver into ganciclovir after oral administration.

Oral bioavailability is ~60%, is taken with food, and elimination is mainly by the kidneys.

Used in the treatment of CMV retinitis in patients with AIDS.

Adverse effects and resistance patterns are similar to those of ganciclovir.

Foscarnet

A pyrophosphate analog that does not require activation (phosphorylation) and inhibits herpesvirus DNA polymerase, RNA polymerase, and HIV reverse transcriptase by blocking pyrophosphate-binding sites of these enzymes.

Available for intravenous administration only; a large volume of fluid is required because of its poor solubility.

Clearance is primarily renal, and ~30% of the drug is deposited in the bones.

Effective in the treatment of CMV retinitis, CMV colitis, CMV esophagitis, acyclovir-resistant HSV infection, and acyclovir-resistant VZV infection.

Can be administered intravitreally in patients having CMV retinitis with AIDS.

Important adverse effects are nephrotoxicity (reduced by preloading with saline and avoidance of other nephrotoxic drugs), electrolyte disturbances (hypocalcemia > hypercalcemia, hypo-/hyperphosphatemia, hypokalemia, hypomagnesemia), genital ulcerations (due to high levels of ionized drug in urine), neurotoxicity (headache, seizures, hallucinations), nausea, vomiting, elevation of hepatic transaminases, anemia, and fatigue.

The risk of hypocalcemia, anemia, and seizures is increased by the co-administration of pentamidine, zidovudine and imipenem, respectively.

Resistance can develop with prolonged use; foscarnet-resistant CMV isolates show cross-resistance to ganciclovir. However, it is effective against ganciclovir-resistant and cidofovir-resistant CMV isolates.

Cidofovir

A cytosine nucleotide analog that, after phosphorylation by host kinases (not viral enzymes), competitively inhibits viral DNA polymerase and gets incorporated into viral DNA chain.

It is active against CMV, HSV, adenovirus, and the human papilloma virus (HPV).

Has two active metabolites - cidofovir diphosphate and cidofovir phosphocholine, having prolonged intracellular half-lives.

Elimination is mainly renal by active tubular secretion.

Used intravenously in the treatment of CMV retinitis, along with probenecid to reduce
its active tubular secretion.

An important adverse effect is proximal tubular nephrotoxicity (reduced by probenecid, dose-adjustment based on creatinine clearance or urinary protein, prehydration with normal saline, and avoidance of other nephrotoxic drugs), including proteinuria, azotemia, metabolic acidosis, and Fanconi’s syndrome; others include neutropenia and ocular toxicity (uveitis, ocular hypotension).

The drug is contraindicated in renal insufficiency.

Cidofovir-resistant isolates show cross-resistance to ganciclovir, but not to foscarnet.

**Fomivirsen**

It is a phosphorothioate oligonucleotide, an antisense agent that interferes with viral gene expression, causing inhibition of viral replication.

It is approved for intravitreal administration for the treatment of CMV retinitis in patients with AIDS, and used when other anti-CMV agents are ineffective.

Important adverse effects are iritis, vitritis, cataract formation, and increased intraocular pressure.

**Review Questions**

The right answers can be found below the references

1. Which of the following anti-influenza drugs is contraindicated in patients with severe asthma?
   - A. Amantadine
   - B. Rimantadine
   - C. Oseltamivir
   - D. Zanamivir
   - E. Peramivir

2. Which of the following drugs used in CMV retinitis can cause severe hypocalcemia?
   - A. Cidofovir
   - B. Fomivirsen
   - C. Foscarnet
   - D. Ganciclovir
   - E. Valganciclovir

3. Which of the following drug is not used in the treatment of influenza?
   - A. Amantadine
   - B. Rimantadine
   - C. Oseltamivir
   - D. Zanamivir
   - E. Sofosbuvir
References


Correct answers: 1D; 2C; 3E

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