Anti-viral and anti-helminthic Drugs

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Learning objectives:

Following the lesson presentation students will be able to:

1. Describe viral replication steps, briefly.
2. Describe the indications, mechanism of action, side effects and contraindications of anti-herpes, anti-cytomegalovirus, anti-retroviral, anti-hepatitis and anti-influenza agents
3. Describe the indications, mechanism of action, side effects and contraindications of anti-nematodes drugs
4. Describe the indications, mechanism of action, side effects and contraindications of anti-trematodes drugs
5. Describe the indications, mechanism of action, side effects and contraindications of anti-cestods drugs

ANTI-VIRAL DRUGS

Viruses are obligate intracellular parasites; their replication depends primarily on synthetic processes of the host cell. Therefore, to be effective, antiviral agents must either block viral entry into or exit from the cell or be active inside the host cell. Viral replication requires several steps (1) attachment of the virus to receptors on the host cell surface; (2) entry of the virus through the host cell membrane; (3) uncoating of viral nucleic acid; (4) synthesis of early regulatory proteins, eg, nucleic acid polymerases; (5) synthesis of new viral RNA or DNA; (6) integration into the nuclear genome; (7) synthesis of late, structural proteins; (8) assembly (maturation) of viral particles; and (9) release from the cell. Antiviral agents can potentially target any of these steps.

AGENTS TO TREAT HERPES SIMPLEX VIRUS (HSV) & VARICELLA-ZOSTER VIRUS (VZV) INFECTIONS

1) Acyclovir

Acyclovir has clinical activity against HSV-1, HSV-2, and VZV, but it is approximately 10 times more potent against HSV-1 and HSV-2 than against VZV. Acyclovir requires three phosphorylation steps for activation. It is converted first to the monophosphate derivative by the virus specified thymidine kinase and then to the di- and triphosphate compounds by host cell enzymes. Because it requires the viral kinase for initial phosphorylation, acyclovir is selectively activated—and the active metabolite accumulates—only in infected cells. Acyclovir triphosphate inhibits viral DNA synthesis by two mechanisms: competition with deoxy GTP for the viral DNA polymerase, resulting in binding to the DNA template as an irreversible complex; and

chain termination following incorporation into the viral DNA. Acyclovir is cleared primarily by glomerular filtration and tubular secretion.

Acyclovir is generally well tolerated, although nausea, diarrhea, and headache may occur. Intravenous infusion may be associated with reversible renal toxicity (ie, crystalline nephropathy or interstitial nephritis) or neurologic effects (eg, tremors, delirium, seizures).

2) Valacyclovir

It is rapidly converted to acyclovir after oral administration via first-pass enzymatic hydrolysis in the liver and intestine, resulting in serum levels that are three to five times greater than those achieved with oral acyclovir and approximate those achieved with intravenous acyclovir. Twice-daily valacyclovir is effective for treatment of first or recurrent genital herpes and varicella and zoster infections; it is approved for use as a 1-day treatment for orolabial herpes and as suppression of frequently recurring genital herpes. Valacyclovir is generally well tolerated, although nausea, headache, vomiting, or rash may occur. At high doses, confusion, hallucinations, and seizures have been reported.

3) Famciclovir

After oral administration, famciclovir is rapidly deacetylated and oxidized by first-pass metabolism to penciclovir. Unlike acyclovir, however, penciclovir does not cause chain termination. Oral famciclovir is effective for the treatment of first and recurrent genital herpes, for chronic daily suppression of genital herpes, for treatment of herpes labialis, and for the treatment of acute zoster. Oral famciclovir is generally well tolerated, although headache, nausea, or diarrhea may occur.

4) Docosanol

Docosanol inhibits fusion between the host cell plasma membrane and the HSV envelope, thereby preventing viral entry into cells and subsequent viral replication. Topical docosanol 10% cream is available without a prescription.

5) Trifluridine

It is phosphorylated intracellularly by host cell enzymes, and then competes with thymidine triphosphate for incorporation by the viral DNA polymerase. Application of a 1% solution is effective in treating keratoconjunctivitis and recurrent epithelial keratitis due to HSV-1 or HSV-2.

AGENTS TO TREAT CYTOMEGALOVIRUS (CMV) INFECTIONS

1) Ganciclovir

Ganciclovir is triphosphorylated to form a nucleotide that inhibits DNA polymerases of cytomegalovirus (CMV), and HSV and causes chain termination. The first phosphorylation step is catalyzed by virus-specific enzymes in both CMV-infected and HSV-infected cells. Ganciclovir is usually given intravenously and penetrates well into tissues, including the eye and CNS. Ganciclovir is used for the prophylaxis and treatment of CMV retinitis and other CMV infections in immunocompromised patients. Systemic toxic effects include leukopenia, thrombocytopenia, mucositis, hepatic dysfunction, and seizures.

2) Valganciclovir

Valganciclovir is a prodrug of ganciclovir. After oral administration, is rapidly hydrolyzed to ganciclovir in the intestinal wall and liver. Valganciclovir is as effective as intravenous ganciclovir for the treatment of CMV retinitis and is also indicated for the prevention of CMV

disease in high-risk solid organ and bone marrow transplant recipients. Adverse effects, drug interactions, and resistance patterns are the same as those associated with ganciclovir.

3) Foscarnet

Foscarnet is a phosphonoformate derivative that does not require phosphorylation for antiviral activity. Although it is not an antimetabolite, foscarnet inhibits viral RNA polymerase, DNA polymerase, and HIV reverse transcriptase. The drug is an alternative for prophylaxis and treatment of CMV infections, including CMV retinitis, and has activity against ganciclovir-resistant strains of this virus. Foscarnet inhibits herpes DNA polymerase in acyclovir-resistant strains that are thymidine kinase–deficient and may suppress such resistant herpetic infections in patients with AIDS. Adverse effects are severe and include nephrotoxicity (30% incidence) with disturbances in electrolyte balance (especially hypocalcemia), genitourinary ulceration, and CNS effects (headache, hallucinations, seizures).

4) Cidofovir

Cidofovir is activated exclusively by host cell kinases. Because phosphorylation does not require viral kinase, cidofovir is active against many acyclovir and ganciclovir-resistant strains. Cidofovir is effective in CMV retinitis, in mucocutaneous HSV infections, including those resistant to acyclovir, and in genital warts. Nephrotoxicity is the major dose-limiting toxicity of cidofovir, additive with other nephrotoxic drugs including amphotericin B and aminoglycoside antibiotics.

ANTIRETROVIRAL AGENTS

1) Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Abacavir, Didanosine Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zalcitabine, Zidovudine (AZT)

To convert their RNA into dsDNA, retroviruses require virally encoded RNA-dependent DNA polymerase (reverse transcriptase). Mammalian RNA and DNA polymerases are sufficiently distinct to permit a selective inhibition of the viral reverse transcriptase. NRTIs are prodrugs converted by host cell kinases to triphosphates, which not only competitively inhibit binding of natural nucleotides to the dNTP-binding site of reverse transcriptase but also act as chain terminators via their insertion into the growing DNA chain.

NRTI agents, taken alone or in combination with other antiretroviral agents, may cause lactic acidemia and severe hepatomegaly with steatosis. Risk factors include obesity, prolonged treatment with NRTIs, and preexisting liver dysfunction. Consideration should be given to suspension of NRTI treatment in patients who develop elevated aminotransferase levels.

2) Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Nevirapine, Delavirdine, Efavirenz, Etravirine

NNRTIs bind to a site on reverse transcriptase different from the binding site of NRTIs. Nonnucleoside drugs do not require phosphorylation to be active and do not compete with nucleoside triphosphates. There is no cross-resistance with NRTIs.

3) Protease Inhibitors (PI)

Indinavir, Ritonavir, Saquinavir, Nelfinavir

The assembly of infectious HIV virions is dependent on an aspartate protease (HIV-1 protease) encoded by the *pol* gene. This viral enzyme cleaves precursor polyproteins to form the final structural proteins of the mature virion core. The HIV protease inhibitors are designer drugs

based on molecular characterization of the active site of the viral enzyme. Protease inhibitors (PIs) have important clinical use in AIDS, most commonly in combinations with reverse transcriptase inhibitors as components of HAART. All of the PIs are substrates and inhibitors of CYP3A4 with ritonavir having the most pronounced inhibitory effect. The PIs are implicated in many drug-drug interactions with other antiretroviral agents and with commonly used medications. The use of PIs in HAART drug combinations has led to the development of disorders in carbohydrate and lipid metabolism. It has been suggested that this is due to the inhibition of lipid-regulating proteins, which have active sites with structural homology to that of HIV protease. The syndrome includes hyperglycemia and insulin resistance or hyperlipidemia, with altered body fat distribution. Buffalo hump, gynecomastia, and truncal obesity may occur with facial and peripheral lipodystrophy. The syndrome has been observed with PIs used in HAART regimens, with an incidence of 30–50% and a median onset time of approximately 1 yr duration of treatment.

4) Entry Inhibitors

Maraviroc, Enfuvirtide

5) Integrase Strand Transfer Inhibitors

Raltegravir

This class of agents binds integrase, a viral enzyme essential to the replication of both HIV-1 and HIV-2. By doing so, it inhibits strand transfer, the third and final step of provirus integration, thus interfering with the integration of reverse-transcribed HIV DNA into the chromosomes of host cells.

AGENTS USED IN VIRAL HEPATITIS

1) Lamivudine, Adefovir, Tenofovir (NRTI)

2) Ribavirin

Ribavirin inhibits the replication of a wide range of DNA and RNA viruses, including influenza A and B, parainfluenza, respiratory syncytial virus (RSV), paramyxoviruses, HCV, and HIV. Although the precise antiviral mechanism of ribavirin is not known, the drug inhibits guanosine triphosphate formation, prevents capping of viral mRNA, and can block RNA-dependent RNA polymerases. Ribavirin is used adjunctively with IFN in chronic HCV infection in patients with compensated liver disease. Monotherapy with ribavirin alone is not effective. Systemic use results in dose-dependent hemolytic anemia.. Ribavirin is a known human teratogen, absolutely contraindicated in pregnancy.

ANTI-INFLUENZA AGENTS

1) Amantadine and Rimantadine

Amantadine and rimantadine inhibit an early step in replication of the influenza A (but not influenza B) virus. They prevent "uncoating" by binding to a protein M2. This protein functions as a proton ion channel required at the onset of infection to permit acidification of the virus core, which in turn activates viral RNA transcriptase. Adamantine-resistant influenza A virus mutants are now common. These drugs are prophylactic against influenza A virus infection and can reduce the duration of symptoms if given within 48 h after contact. The H1N1 strain responsible for the recent pandemic that contain genes derived from both avian and porcine influenza viruses is also resistant to the adamantines. Fortunately, there is minimal cross-resistance to the neuraminidase inhibitors. Toxic effects of these agents include GI irritation, dizziness, ataxia,

and slurred speech. Rimantadine's activity is no greater than that of amantadine, but it has a longer half-life and requires no dosage adjustment in renal failure.

2) Oseltamivir and Zanamivir

These drugs are inhibitors of neuraminidases produced by influenza A and B and are currently active against both H3N2 and H1N1 strains. These viral enzymes cleave sialic acid residues from viral proteins and surface proteins of infected cells. They function to promote virion release and to prevent clumping of newly released virions. By interfering with these actions, neuraminidase inhibitors impede viral spread. Oseltamivir is a prodrug used orally, activated in the gut and the liver. Zanamivir is administered intranasally. Both drugs decrease the time to alleviation of influenza symptoms and are more effective if used within 24 h after onset of symptoms. Taken prophylactically, oseltamivir significantly decreases the incidence of influenza. GI symptoms may occur with oseltamivir; zanamivir may cause cough and throat discomfort and has induced bronchospasm in asthmatic patients.

ANTIHELMINTHIC DRUGS

DRUGS THAT ACT AGAINST NEMATODES

The medically important intestinal nematodes responsive to drug therapy include *Enterobius vermicularis* (pinworm), *Trichuris trichiuria* (whipworm), *Ascaris lumbricoides* (roundworm), *Ancyclostoma* and *Necator* species (hookworms), and *Strongyloides stercoralis* (threadworm). More than 1 billion persons worldwide are estimated to be infected by intestinal nematodes. Pinworm infections are common throughout the United States, and hookworm and threadworm

are endemic in the southern United States. Tissue nematodes responsive to drug therapy include *Ancyclostoma* species, which cause cutaneous larva migrans. Species of *Dracunculus, Onchocerca, Toxocara,* and *Wuchereria bancrofti* (the cause of filariasis) all are responsive to drug treatment. The number of persons worldwide estimated to be infected by tissue nematodes exceeds 0.5 billion.

1) Albendazole

The action of albendazole is thought to involve inhibition of microtubule assembly. The drug is larvicidal in ascariasis, cystercercosis, hookworm, and hydatid disease and is ovicidal in ascariasis, ancyclostomiasis, and trichuriasis. Albendazole has a wide antihelminthic spectrum. It is a primary drug for ascariasis, hookworm, pinworm, and whipworm infections and an alternative drug for treatment of threadworm infections, filariasis, and both visceral and cutaneous larva migrans. Albendazole is also used in hydatid disease and is active against the pork tapeworm in the larval stage (cysticercosis).

Toxicity: Albendazole has few toxic effects during short courses of therapy (1–3 d). However, a reversible leukopenia, alopecia, and elevation of liver function enzymes can occur with more prolonged use. Long-term animal toxicity studies have described bone marrow suppression and fetal toxicity. The safety of the drug in pregnancy and young children has not been established.

2) Diethylcarbamazine

Diethylcarbamazine immobilizes microfilariae by an unknown mechanism, increasing their susceptibility to host defense mechanisms. Diethylcarbamazine is the drug of choice for several filarial infections including those caused by *Wucheria bancrofti* and *Brugia malayi* and for eye worm disease (loa loa).

Toxicity: Adverse effects include headache, malaise, weakness, and anorexia. Reactions to proteins released by dying filariae include fever, rashes, ocular damage, joint and muscle pain, and lymphangitis.

3) Ivermectin

Ivermectin intensifies GABA-mediated neurotransmission in nematodes and causes immobilization of parasites, facilitating their removal by the reticuloendothelial system. Selective toxicity results because in humans GABA is a neurotransmitter only in the CNS, and ivermectin does not cross the blood-brain barrier. Ivermectin is the drug of choice for onchocerciasis, cutaneous larva migrans, strongyloidiasis, and some forms of filariasis.

Toxicity: Single-dose oral treatment in onchocerciasis results in reactions to the dying worms, including fever, headache, dizziness, rashes, pruritus, tachycardia, hypotension, and pain in joints, muscles, and lymph glands. These symptoms are usually of short duration, and most can be controlled with antihistamines and nonsteroidal anti-inflammatory drugs. Avoid other drugs that enhance GABA activity. Ivermectin should not be used in pregnancy.

4) Mebendazole

Mebendazole acts by selectively inhibiting microtubule synthesis and glucose uptake in nematodes. Mebendazole is a primary drug for treatment of ascariasis and for pinworm and whipworm infections. Mebendazole has also been used as a backup drug in visceral larval migrans. Less than 10% of the drug is absorbed systemically after oral use, and this portion is metabolized rapidly by hepatic enzymes. Plasma levels may be decreased by carbamazepine or phenytoin and increased by cimetidine.

Toxicity: Mebendazole toxicity is usually limited to gastrointestinal irritation, but at high doses agranulocytopenia and alopecia have occurred. The drug is teratogenic in animals and therefore contraindicated in pregnancy.

5) Piperazine

Piperazine paralyzes ascaris by acting as an agonist at GABA receptors. The paralyzed roundworms are expelled live by normal peristalsis. Piperazine is an alternative drug for ascariasis.

Toxicity: Mild gastrointestinal irritation is the most common side effect. Piperazine should not be used in pregnant patients or those with hepatic or renal dysfunction or seizure disorders.

6) Pyrantel Pamoate

Pyrantel pamoate stimulates nicotinic receptors present at neuromuscular junctions of nematodes. Contraction of muscles occurs, followed by a depolarization-induced paralysis. The drug has no actions on flukes or tapeworms. Pyrantel pamoate has wide activity against nematodes killing adult worms in the colon but not the eggs. It is a drug of choice for hookworm and roundworm infections and an alternative drug for pinworms. The drug is poorly absorbed when given orally.

Toxicity: Adverse effects are minor but include gastrointestinal distress, headache, and weakness. Use with caution in patients with hepatic dysfunction.

7) Thiabendazole

Thiabendazole is a structural congener of mebendazole and has a similar action on microtubules. Because of its adverse effects, thiabendazole is an alternative drug in strongyloidiasis and trichinosis (adult worms).

Toxicity: Thiabendazole is much more toxic than other benzimidazoles or ivermectin, so these other drugs are preferred. Its toxic effects include gastrointestinal irritation, headache, dizziness, drowsiness, leukopenia, hematuria, and allergic reactions, including intrahepatic cholestasis. Reactions caused by dying parasites include fever, chills, lymphadenopathy, and skin rash. Irreversible liver failure and fatal Stevens-Johnson syndrome have also been reported. Avoid in pregnant patients or those with hepatic or renal disease.

DRUGS THAT ACT AGAINST TREMATODES

The medically important trematodes include *Schistosoma* species (blood flukes, estimated to affect more than 150 million persons worldwide), *Clonorchis sinensis* (liver fluke, endemic in Southeast Asia), and *Paragonimus westermani* (lung fluke, endemic to both Asia and the Indian subcontinent). With few exceptions, fluke infections respond well to praziquantel.

1) Praziquantel

Praziquantel increases membrane permeability to calcium, causing marked contraction initially and then paralysis of trematode and cestode muscles; this is followed by vacuolization and parasite death. Praziquantel has a wide antihelminthic spectrum that includes activity in both trematode and cestode infections. It is the drug of choice in schistosomiasis (all species), clonorchiasis, and paragonimiasis and for infections caused by small and large intestinal flukes. The drug is active against immature and adult schistosomal forms. Praziquantel is also 1 of 2 drugs of choice (with niclosamide) for infections caused by cestodes (all common tapeworms) and an alternative agent (to albendazole) in the treatment of cysticercosis.

Toxicity: Common adverse effects include headache, dizziness and drowsiness, malaise, and, less frequently, gastrointestinal irritation, skin rash, and fever. Neurologic effects can occur in the treatment of neurocyticercosis including intracranial hypertension and seizures. Corticosteroid therapy reduces the risk of the more serious reactions. Praziquantel is contraindicated in ocular cysticercosis. In animal studies, the drug increased abortion rate.

2) Bithionol

Bithionol is a codrug of choice (with triclabendazole) for treatment of fascioliasis (sheep liver fluke) and an alternative agent in paragonimiasis. The mechanism of action of the drug is unknown.

Toxicity: Common adverse effects of bithionol include nausea and vomiting, diarrhea and abdominal cramps, dizziness, headache, skin rash (possibly a reaction to dying worms), and phototoxicity. Less frequently, pyrexia, tinnitus, proteinuria, and leukopenia may occur.

3) Metrifonate

Metrifonate is an organophosphate prodrug that is converted in the body to the cholinesterase inhibitor dichlorvos. The active metabolite acts solely against *Schistosoma haematobium* (the cause of bilharziasis). Toxic effects occur from excess cholinergic stimulation. The drug is contraindicated in pregnancy.

4) Oxamniquine

Oxamniquine is effective solely in *Schistosoma mansoni* infections (intestinal bilharziasis), acting on male immature forms and adult schistosomal forms. The drug causes paralysis of the worms, but its precise mechanism is unknown. Dizziness is a common adverse effect (no driving

for 24 h); headache, gastrointestinal irritation, and pruritus may also occur. Reactions to dying parasites include eosinophilia, urticaria, and pulmonary infiltrates. It is not advisable to use the drug in pregnancy or in patients with a history of seizure disorders.

DRUGS THAT ACT AGAINST CESTODES (TAPEWORMS)

The 4 medically important cestodes are *Taenia saginata* (beef tapeworm), *Taenia solium* (pork tapeworm, which can cause cysticerci in the brain and the eyes), *Diphyllobothrium latum* (fish tapeworm), and *Echinococcus granulosus* (dog tapeworm, which can cause hydatid cysts in the liver, lungs, and brain). The primary drugs for treatment of cestode infections are praziquantel (see prior discussion) and niclosamide.

1) Niclosamide

Niclosamide may act by uncoupling oxidative phosphorylation or by activating ATPases. Niclosamide is an alternative drug to praziquantel for infections caused by beef, pork, and fish tapeworm. It is not effective in cysticercosis (for which albendazole or praziquantel is used) or hydatid disease caused by *Echinococcus granulosus* (for which albendazole is used). Scoleces and cestode segments are killed, but ova are not. Niclosamide is effective in the treatment of infections from small and large intestinal flukes.

Toxicity: Toxic effects are usually mild but include gastrointestinal distress, headache, rash, and fever. Some of these effects may result from systemic absorption of antigens from disintegrating parasites. Ethanol consumption should be avoided for 24–48 h.

Reference:

Katzung BG and Trevor AG. Basic and Clinical Pharmacology, McGraw-Hill, 13th edition, 2015.

MCQ: An AIDS patient, who is being treated with multiple drugs, develops central adiposity, hyperlipidemia and insulin resistance. If these changes are related to his drug treatment, this drug belongs to which group of anti-retroviral drugs?

a) Nucleoside Reverse Transcriptase Inhibitors (NRTIS)

b) Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIS)

c) Protease Inhibitors

d) Fusion Inhibitors

e) Integrase Inhibitors