Chapter 8: Antifungal and Antiviral Agents

Antifungal Agents

- Haveles (p. 102)
- Antibiotics and antifungals are effective against a certain spectrum of organisms: bacteria, protozoa, rickettsia, trichomonads, amoebas, and spirochetes
- They are not effective against either fungal or viral infections

Antifungal Agents

- Haveles (pp. 102-103) (Tables 8-1, 8-2)
- They can be divided into those that affect primarily the skin and mucosa and those that affect the whole body
- Mucosal lesions may be treated with a topical or systemic antifungal agent
- Two common groups are the candida-like and tinea
- Mucocutaneous candidal infections are managed with nystatin, clotrimazole, ketoconazole, or fluconazole
- Tinea affects the skin and produces athlete's foot, "jock itch," and ringworm; managed both with prescription and over-the-counter medications

Cont'd…
Antifungal Agents

- Haveles (pp. 102-103, 106) (Figs. 8-1, 8-2)
- Systemic mycoses produced by fungi include aspergillosis, blastomycosis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, and paracoccidioidomycosis
- Chromomycosis, mycetoma, and sporotrichosis may progress to deep mycotic infections
- These serious infections are medical management situations
  - Amphotericin B and miconazole are used to treat them

Nystatin

- Not absorbed from the mucous membranes or through intact skin
- Taken orally, it is poorly absorbed from the gastrointestinal (GI) tract
- Fungicidal and fungistatic against a variety of yeasts and fungi

Nystatin

- Adverse reactions are minor and infrequent
  - Applied topically or taken orally, little absorption occurs
  - With higher doses, nausea, vomiting, and diarrhea have occasionally occurred

Nystatin

- Haveles (pp. 103-104) (Table 8-1)
- Used for both treatment and prevention of oral candidiasis in susceptible cases
  - Candida albicans is a frequent inhabitant of the oral cavity; only under unusual conditions does it produce disease
  - Affected patients are often immunocompromised

Nystatin

- Haveles (p. 103) (Table 8-1)
- For treatment of oral candidiasis; available as an aqueous suspension containing 50% sucrose
  - Swish, swirl, and spit or swallow 5 ml four times daily
    - The suspension should remain in the mouth for 2 minutes for the best effect
Nystatin

- Nystatin pastilles (contain sugar)
  - 15 minutes to dissolve, bathing lesions in antifungal agent for a longer period
  - Used four times daily
- The products are used for between 10 and 14 days or for 48 hours after the symptoms have subsided and cultures have returned negative

Examples

- Haveles (p. 103) (Table 9-1)
- Nystatin (Mycostatin, Nilstat, others)

Imidazoles

- Haveles (pp. 104-105)
- Several imidazoles useful in dentistry include clotrimazole, miconazole, fluconazole, and itraconazole

Clotrimazole

- Indicated for the local treatment of oropharyngeal candidiasis
  - Usual adult dose is one lozenge five times daily for 10 to 14 days or for 48 hours after symptoms have cleared

Ketoconazole

- Haveles (pp. 104-105)
- A synthetic antifungal agent available as a slowly dissolving, sugar-containing lozenge for oral use
  - Mechanism of action involves alteration of cell membrane permeability
  - Spectrum of action is primarily against the *Candida* species
  - Most common adverse reactions involve the GI tract, including abdominal pain, diarrhea, and nausea
  - Indicated for systemic fungal infections, including blastomycosis, candidiasis, coccidioidomycosis, and histoplasmosis
Ketoconazole

- Haveles (p. 105)

- Adverse reactions of ketoconazole
  - GI effects: the most frequent adverse reactions are nausea and vomiting
  - Hepatotoxicity effects: the most serious adverse reaction; thought to be idiosyncratic
  - Other effects: headache, dizziness, drowsiness, photophobia, skin rash or pruritus, and insomnia
  - Pregnancy and nursing considerations: can produce syndactyly, oligodactyly, dystocia, and embryotoxicity

Ketoconazole

- Haveles (p. 105)

- Drug interactions
  - Many, because an acidic environment is required, agents that alter the amount of stomach acid could theoretically reduce the absorption of ketoconazole
  - Ketoconazole inhibits the CYP P-450 3A4 hepatic microsomal isoenzyme, which can produce drug interactions with many other drugs also metabolized by this isoenzyme

Uses of Ketoconazole

- Haveles (p. 105)

- Dental: indicated for treatment and management of mucocutaneous and oropharyngeal candidiasis (oral thrush)
  - Used only after topical antifungal agents have been ineffective or its believed they will be ineffective
- Medical: indicated for treatment of candidiasis, histoplasmosis, and paracoccidioidomycosis
  - Used to treat recalcitrant cutaneous dermatophytoses such as tinea corporis, tinea cruris, tinea versicolor, and seborrheic dermatitis

Dose of Ketoconazole

- Haveles (p. 105)

- Dose for treatment of Candida is 200 to 400 mg orally daily
  - Used for at least 2 weeks; 6 to 12 months may be required for chronic mucocutaneous candidiasis
  - Available for topical administration in a 2% aqueous vehicle (cream) for tinea or candidal infections
  - A shampoo is used twice weekly for dandruff, a condition caused by the fungus

Other Imidazoles

- Haveles (p. 105)

- Other imidazoles are used to treat certain fungal infections
  - Fluconazole prevents the synthesis of ergosterol in the fungal cell membrane by inhibiting fungal cytochrome P-450 enzymes
    - Indicated for the treatment of oropharyngeal and esophageal candidiasis, and serious systemic fungal infections

Other Imidazoles

- Haveles (p. 105)

- Itraconazole is used for blastomycosis, histoplasmosis, and aspergillosis
  - The first antifungal effective in the treatment of onychomycosis of the toenail or fingernail
Examples of Antifungal Agents

- Haveles (p. 103) (Table 8-1)
  - Fluconazole (Diflucan)

Other Antifungal Agents

- Haveles (pp. 105-106)
  - Amphotericin B
    - Used in the treatment of many serious systemic fungal infections
    - Because of side effects it is nicknamed “amphoterrible”

Other Antifungal Agents

- Amphotericin B
  - An amphoteric polyene macrolide antibiotic produced by *Streptomyces nodosus*
    - Binds to the sterols in the fungus cell membrane, altering membrane permeability
    - Spectrum includes many fungi such as certain strains of *Aspergillus, Paracoccidioides, Coccidioides, Cryptococcus, Histoplasma, Mucor, and Candida*
    - Also effective against the protozoa *Leishmania*

Other Antifungal Agents

- Griseofulvin
  - An antibiotic produced by *Penicillium griseofulvum*
    - Disrupts the cells mitotic spindle structure and arrests cell division in metaphase
    - Preferentially deposited in diseased keratin precursors (hair, nails, skin)

Other Antifungal Agents

- Griseofulvin
  - Spectrum includes tineas (e.g. ringworm), *Trichophyton, Microsporum*, and *Epidermophyton*
    - but does not include *Candida* organisms
  - Adverse reactions include headache, GI complaints, and overgrowth of *Candida* organisms in the oral cavity
  - Hypersensitivity reactions include urticaria, photosensitivity, and lupus-like reactions
  - Indicated for treatment of susceptible infections of the skin, hair, and nails
  - The drug is deposited only in growing tissues
Antiviral Agents

- Herpes simplex
  - Acyclovir
  - Docosanol 10%
  - Penciclovir
  - Famciclovir
- Acquired immunodeficiency syndrome (AIDS)
  - Nucleoside reverse transcriptase inhibitors
  - Nonnucleoside reverse transcriptase inhibitors
  - Protease inhibitors
  - Combinations
  - Other antiviral agents

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Herpes Simplex

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- Most antiviral agents are either purine or pyrimidine analogues that inhibit deoxyribonucleic acid (DNA) synthesis

acyclovir (Zovirax)

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- A purine nucleoside
  - The triphosphate form exerts its antiviral action on herpesviruses by interfering with DNA polymerase and inhibiting DNA replication
  - It is much less toxic to normal cells because it is preferentially taken up by infected cells

acyclovir (Zovirax)

- Herpes viruses are associated with “cold sores”
- Most antiviral agents are either purine or pyrimidine analogues that inhibit deoxyribonucleic acid (DNA) synthesis
- Pharmacokinetics
  - Taken orally, between 15% and 30% is absorbed; widely distributed throughout the body and excreted primarily unchanged in the urine
  - Spectrum
  - Herpesviruses, including herpes simplex types 1 and 2, varicella zoster, Epstein-Barr, Herpesvirus simiae (B virus), and cytomegalovirus

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- Adverse reactions
  - Topical administration: produces burning, stinging, or mild pain in about one third of patients
  - Oral administration: headache (13%) is one of the most common; other central nervous system (CNS) and GI effects
  - Parenteral administration: local reactions at the injection site are the most common
acyclovir (Zovirax)

Haveles (pp. 107, 109)

- **Uses**
  - **Topical**
    - Indications include initial herpes genitalis and limited non-life-threatening initial and recurrent mucocutaneous herpes simplex virus 1 and 2 (HSV-1 and HSV-2) in immunocompromised persons
  - **Oral**
    - Indicated for treatment of initial herpes genitalis and management of recurrent herpes genitalis infections in both immunocompromised and nonimmunocompromised patients
  - **Injectable**
    - Used for severe initial herpes genitalis infections in the immunocompromised patient

- **Dose**
  - Oral adult dose for treatment of initial genital herpes is 200 mg every 4 hours while the patient is awake, five times daily for 10 days
  - Acyclovir has not been shown to effectively treat herpes labialis in topical, tablet, or capsule form.

Docosanol 10%

Haveles (p. 109)

- Available topically and without a prescription
- Has been shown to decrease healing time by about a half day in patient with recurrent orolabial herpes when started within 12 hours of the appearance of prodromal symptoms

Penciclovir

Haveles (p. 109)

- Available topically
- Shown to reduce both the duration of the lesion and the pain of the lesions on the lips and face associated with both primary and recurrent herpes simplex

Famciclovir

Haveles (p. 109)

- Famciclovir and valacyclovir are prodrugs that are converted to penciclovir and acyclovir as they pass through the intestinal wall.
- Indicated in the treatment of recurrent episodes of genital herpes, for treatment of acute localized varicella-zoster infections.
- Ganciclovir is indicated for serious cytomegalovirus retinitis in immunocompromised patients

Acquired Immunodeficiency Syndrome

Haveles (pp. 109-110) (Tables 8-4, 8-5)

- Antiretroviral agents are used in combinations called “cocktails” to manage AIDS
- They include nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors.
- The usual combination includes one choice from each of the three groups.

cont’d…
Acquired Immunodeficiency Syndrome

- Opportunistic infections often occur in patients with AIDS
  - They may be taking various antiinfective agents to prevent tuberculosis, Pneumocystis carinii pneumonia, herpes infections, and candidiasis

Nucleoside Reverse Transcriptase Inhibitors

- Zidovudine is converted into zidovudine triphosphate and then incorporated into DNA polymerase so that synthesis of viral DNA is terminated
  - Azidothymidine (AZT) is well absorbed orally, metabolized by the liver, and excreted by the kidneys
  - Distributed to most body tissue

Nucleoside Reverse Transcriptase Inhibitors

- Toxicity of AZT is related to bone marrow depression
- CNS effects include headache, agitation and insomnia
- Oral manifestations reported include taste perversion, edema of the tongue, bleeding gums, and mouth ulcers
- Acetaminophen, indomethacin, and aspirin can inhibit AZT’s glucuronidation and potentiate the toxicity of both drugs

Nonnucleoside Reverse Transcriptase Inhibitors

- Nevirapine, an NNRTI, is specific for human immunodeficiency virus type 1 (HIV-1)
  - These agents inhibit the same enzymes as the nucleoside analogues but do not require bioactivation
  - Adverse reactions include CNS effects, rash, GI effects, and elevated liver function tests

Protease Inhibitors

-Saquinavir prevents the cleavage of viral protein precursors needed to generate functional structural proteins in and modulation of reverse transcriptase activity, preventing the maturation of HIV-infected cells
- Protease inhibitors can interfere with the action of HIV infected cells, whereas the previous two groups of drugs cannot

Protease Inhibitors

- Adverse reactions include rash, hyperglycemia, and paresthesias
- GI adverse reactions include pain, diarrhea, and vomiting
- Oral adverse reactions involve buccal mucosa alteration
Combinations

- Haveles (p. 110)
  - The combinations of drugs used to manage HIV or AIDS are constantly changing
  - Normally, patients with HIV will be taking an NRTI, an NNRTI, and a protease inhibitor

Other Antiviral Agents

- Haveles (pp. 110-111)
  - amantadine (Symmetrel): inhibits the penetration of the absorbed virus into the host’s cells or inhibits the uncoating of the influenza A viruses
  - Side effects include nausea, dizziness, lightheadedness, and insomnia
  - Can be used to prevent or for treatment to reduce symptoms of influenza A viruses

Examples of Drugs Used to Treat Human Immunodeficiency Virus

- Haveles (p. 109) (Table 8-4)
  - Nucleoside analogues
    - didanosine (ddl) (Videx)
    - lamivudine (3TC) (Epivir)
    - stavudine (d4T) (Zerit)
    - zalcitabine (ddC) (Hivid)
    - zidovudine (AZT, ZVD) (Retrovir)
  - Nonnucleoside Analogs
    - delavirdine (Rescriptor)
    - nevirapine (NVP) (Viramune)
  - Protease Inhibitors
    - indinavir (Crixivan)
    - nelfinavir (Viracept)
    - ritonavir (Norvir)
    - saquinavir (Invirase, Fortovase)

Other Antiviral Agents

- Haveles (pp. 110-111)
  - Interferons
    - A large group of endogenous proteins that have antiviral, cytotoxic, and immunomodulating action
      - Recombinant DNA technology now produces interferons

Examples of Interferons

- Haveles (p. 110) (Table 8-6)
  - alfa-2a (Roferon-A)
  - peginterferon alfa-2a (Pegasys)
  - peginterferon alfa-2a with ribavirin (Copegus)
  - alfa-2b (Intron-A)
  - peginterferon alfa-2b (PEG-Intron)
  - peginterferon alfa-2b plus ribavirin (Rebetol)
  - alfa-n3 (Alferon N)
  - beta-1a (Avonex)
  - beta-1b (Betaseron)